An Evolving Landscape in Schizophrenia:

A Discussion of Novel and Emerging Mechanisms of Action

Psych Congress MasterClass

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Faculty Disclosure

- **Booke Kempf**: has been a consultant and/or advisor to or has received honoraria from: AbbVie, Alkermes, Allergan, Axsome, Biogen, Intracellular Therapies, Janssen, Lundbeck, Otsuka, Sage, Takeda, Teva.

- **Dr. Correll**: has been a consultant and/or advisor to or has received honoraria from: AbbVie, Acadia, Alkermes, Allergan, Angelini, Aristo, Biogen, Boehringer-Ingelheim, Cardio Diagnostics, Cerevel, CNX Therapeutics, Pathways, Darnitsa, Denovo, Gedeon Richter, Hikma, Holmusk, IntraCellular Therapies, Jamjoom Pharma, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedInCell, Merck, Mindpax, Mitsubishi, Tanabe Pharma, Mylan, Neurocrine, Neurelis, Newron, Noven, Novo Nordisk, Otsuka, Pharmabrain, PPD Biotech, Recordati, Relmada, Reviva, Rovi, Sage, Seqirus, SK Life Science, Sumitomo Pharma America, Sunovion, Sun Pharma, Supernus, Takeda, Teva, Tolmar, Vertex, and Viatris. He provided expert testimony for Janssen and Otsuka. He served on a Data Safety Monitoring Board for Compass Pathways, Denovo, Lundbeck, Relmada, Reviva, Rovi, Supernus, and Teva. He has received grant support from Janssen and Takeda. He received royalties from UpToDate and is also a stock option holder of Cardio Diagnostics, Kuleon Biosciences, LB Pharma, Mindpax, and Quantic.

Disclosure

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).

- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.

- This activity has been independently reviewed for balance.

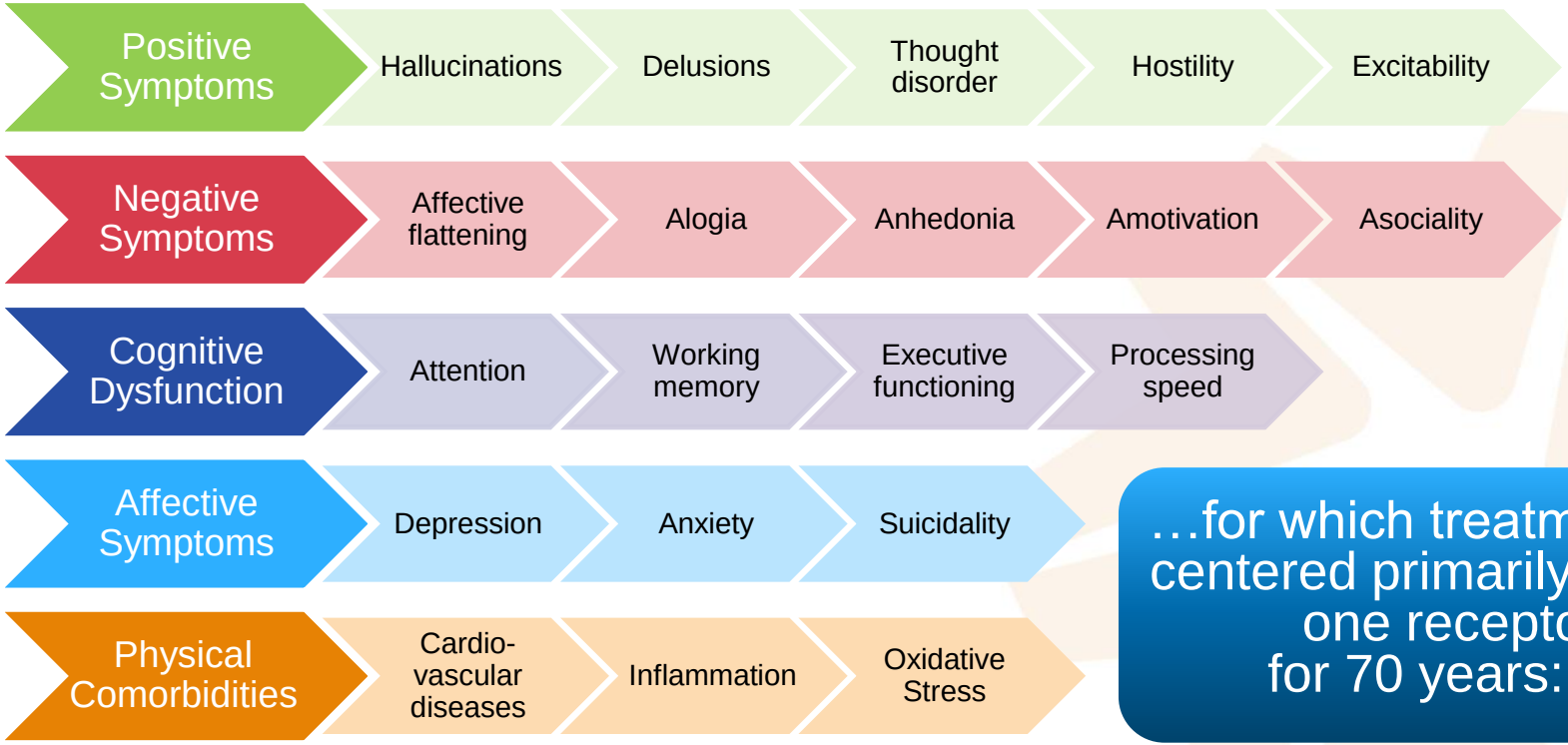
Learning Objectives

- Assess the challenges associated with antipsychotics for schizophrenia that act as D2 receptor antagonists, including inadequate response, adverse effects, and nonadherence/discontinuation
- Describe the MOAs of novel and investigational agents, including TAAR1 agonists, M1/M4 receptor agonists, and VMAT2 inhibitors, and how they may address shortcomings associated with conventional treatments
- Evaluate the most recent clinical trial data associated with the safety, tolerability, and efficacy of novel and investigational agents for patients with schizophrenia

Schizophrenia Overview and Challenges

Brooke Kempf, PMHNP-BC

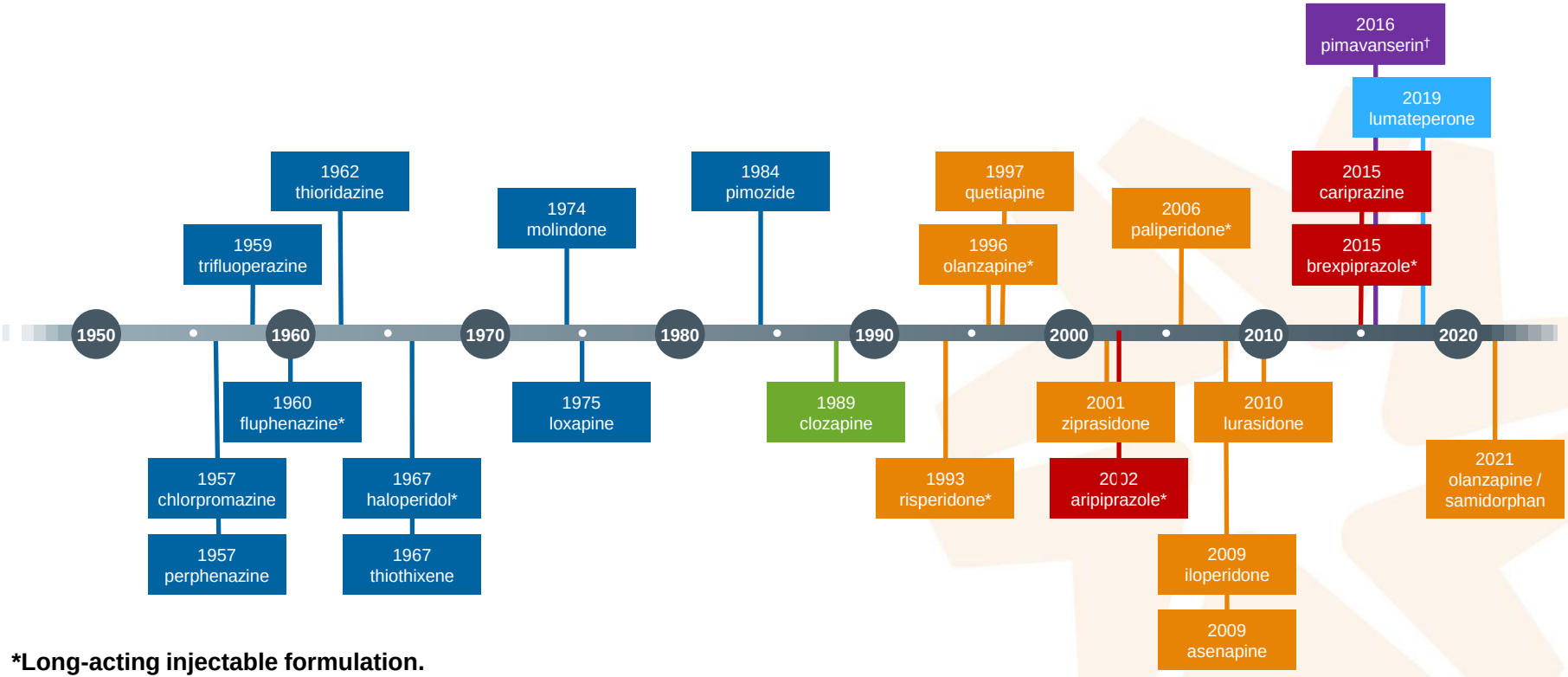
Schizophrenia is a Multidimensional Illness…



…for which treatment has centered primarily around one receptor for 70 years: D_2

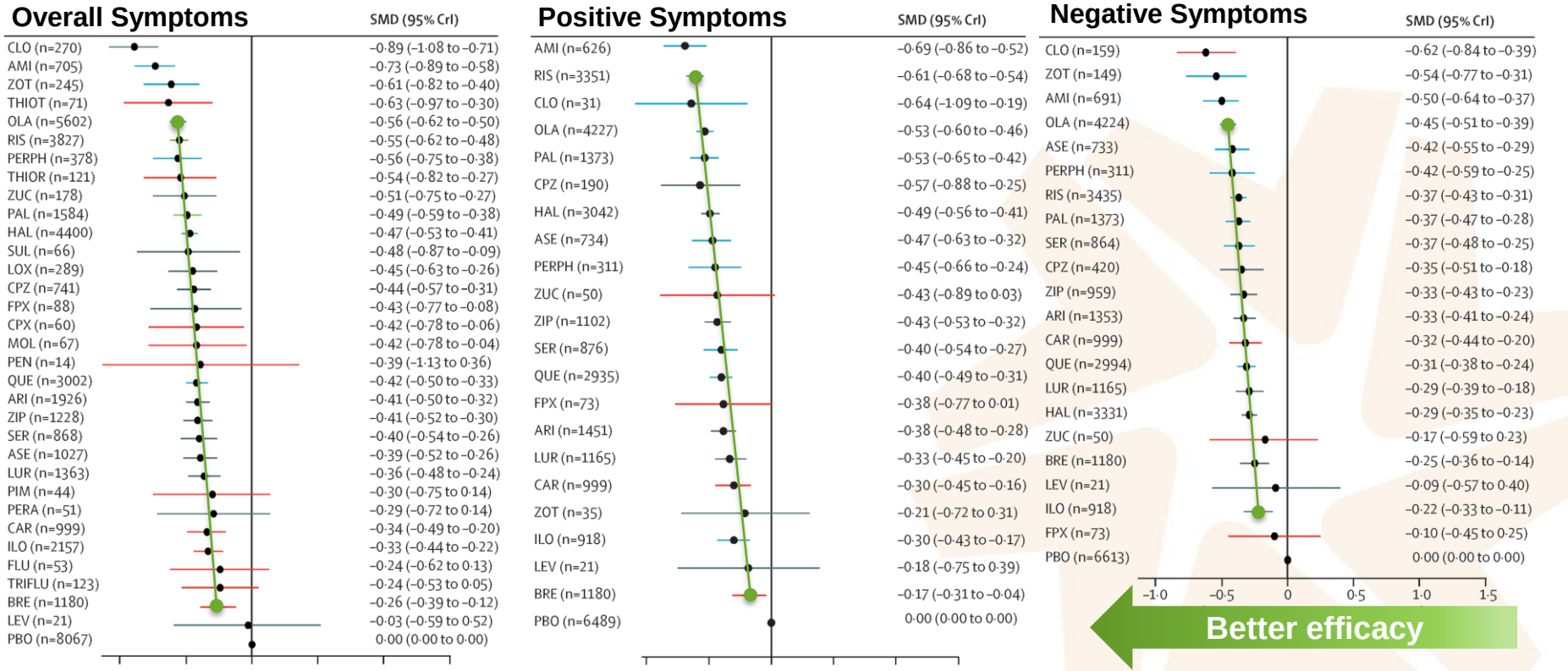
Carbon, et al. *CNS Spectr*. 2014;19:38. Millan, et al. *Eur Neuropsychopharmac*ol. 2014;24:645. Morrens, et al. *Front Psychiatry*. 2014;5:145. Millan, et al. *Nat Rev Drug Discov*. 2012;11:141. Ventriglio, et al. *Front Psychiatry*. 2016;7:116. Pillinger, et al. *Mol Psychiatry*. 2019;24:928.

Timeline of FDA-Approved Antipsychotics



***Long-acting injectable formulation.**
†Approved for psychosis associated with Parkinson disease only.
Adapted from: https://thestarr.org/wp-content/uploads/TimelineofFDA-ApprovedAntipsychotics-1.jpg

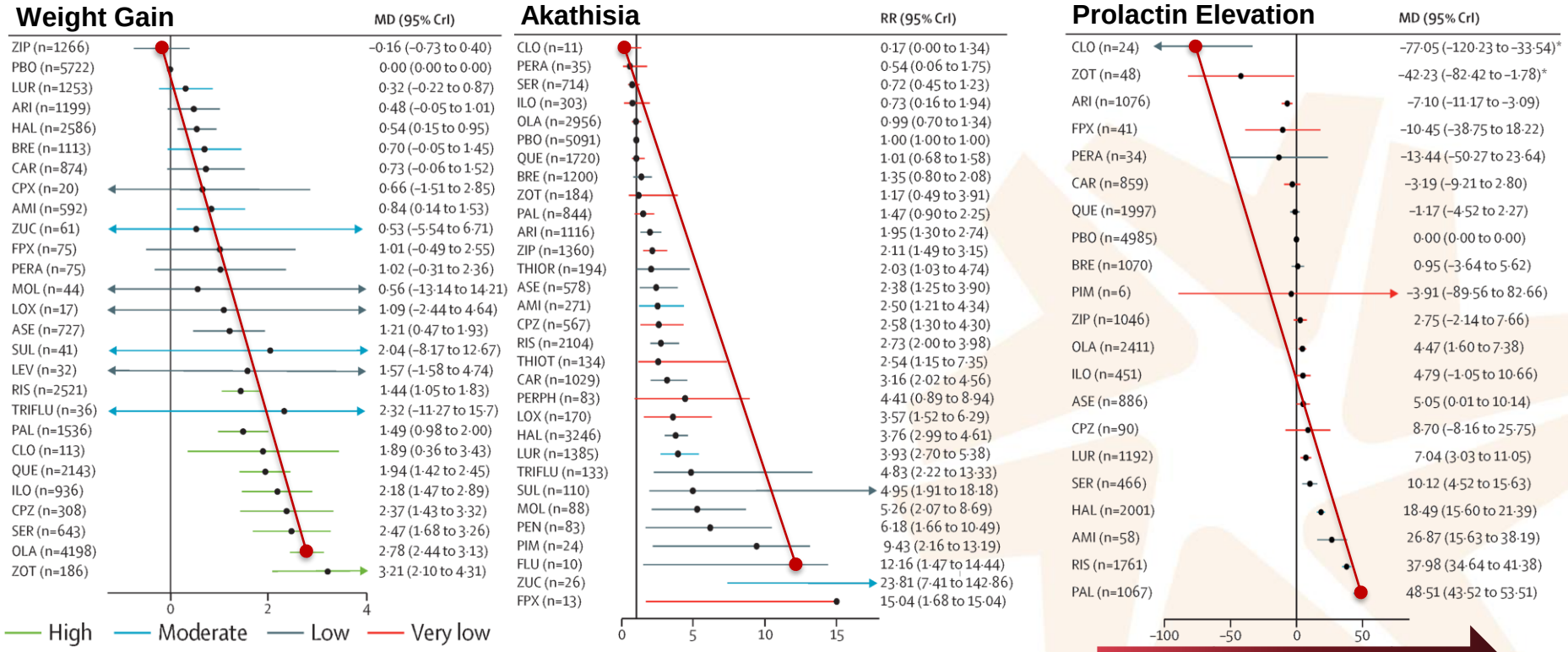
Little Variability of Efficacy in Current Treatments



Trend lines include highest and lowest ranked agents in US, except clozapine

Huhn M, et al. *The Lancet*. 2019;394(10202):939-951.

More Distinguishable in Side Effects



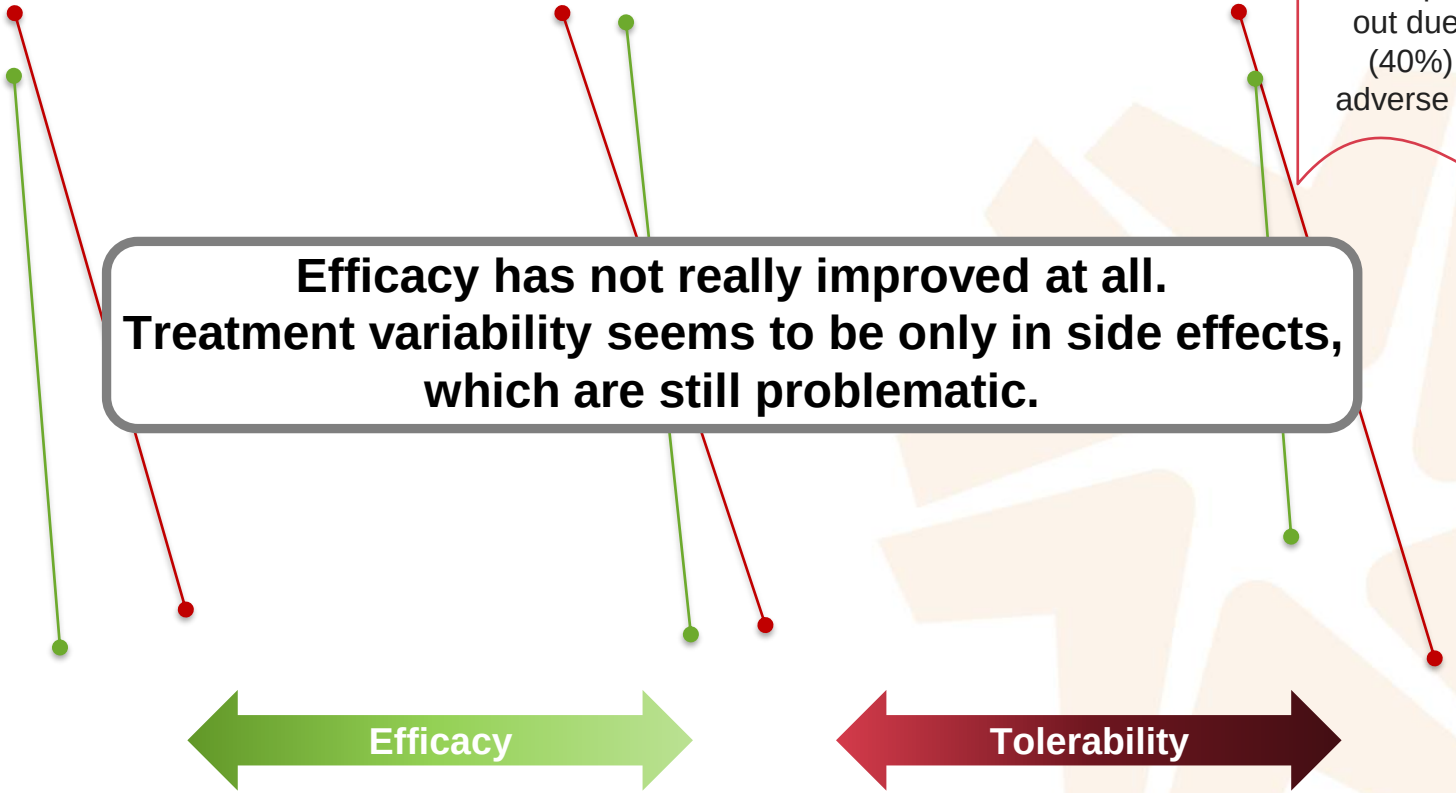
Trend lines include highest and lowest ranked agents in US

Huhn M, et al. *The Lancet*. 2019;394(10202):939-951.

Reading Between the Lines

*more patients dropped out due to inefficacy (40%) than due to adverse events (20%)

Efficacy has not really improved at all.
Treatment variability seems to be only in side effects, which are still problematic.

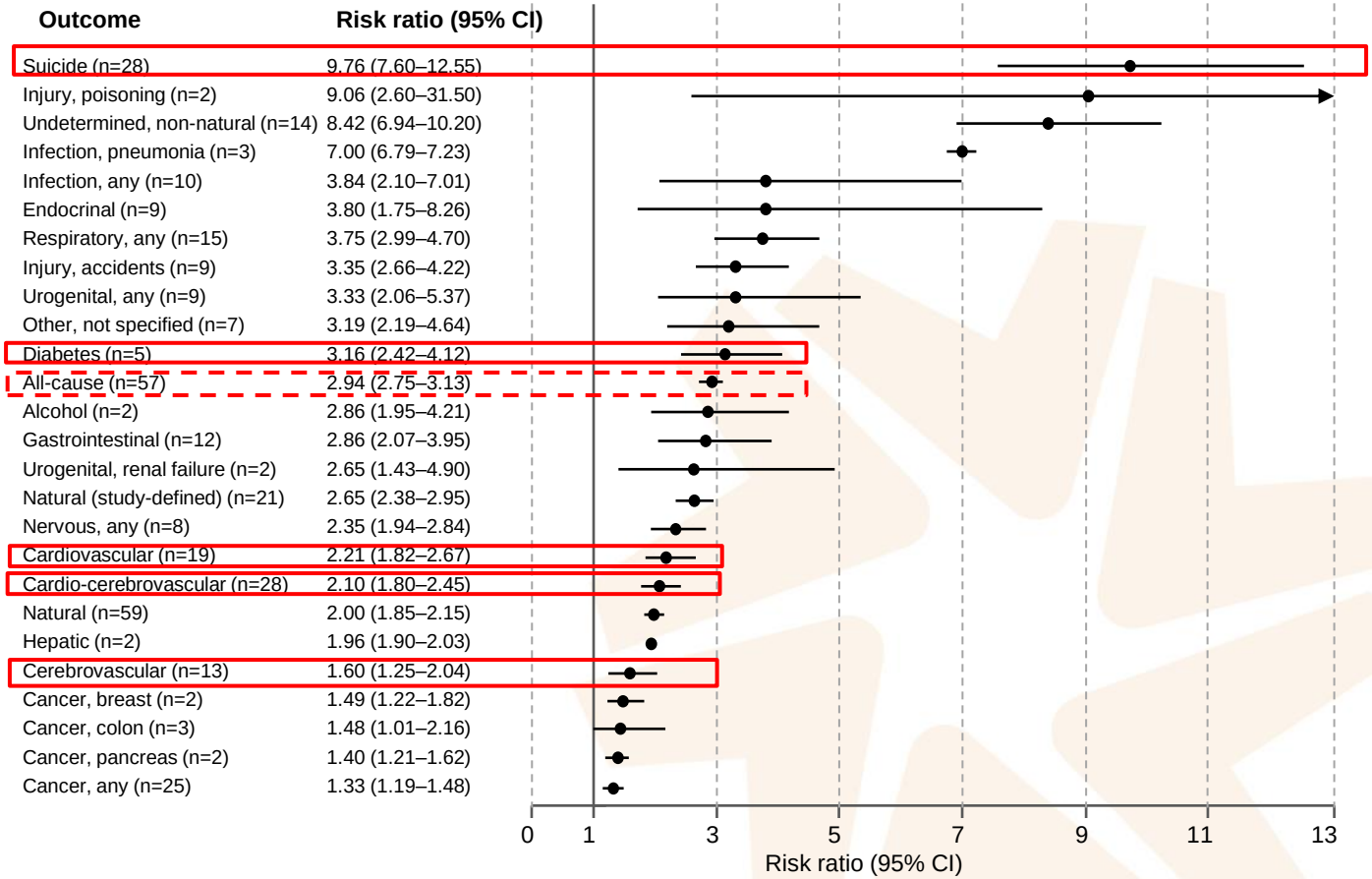


Huhn M, et al. *The Lancet*. 2019;394(10202):939-951.

Network Meta-analysis of 18 Antipsychotics for Acute Exacerbation of Schizophrenia: Cardiometabolic Risk Heat Map

100 randomized controlled trials; 25,925 patients.
Pillinger T, et al. *Lancet Psychiatry.* 2020 Jan;7(1):64-77.

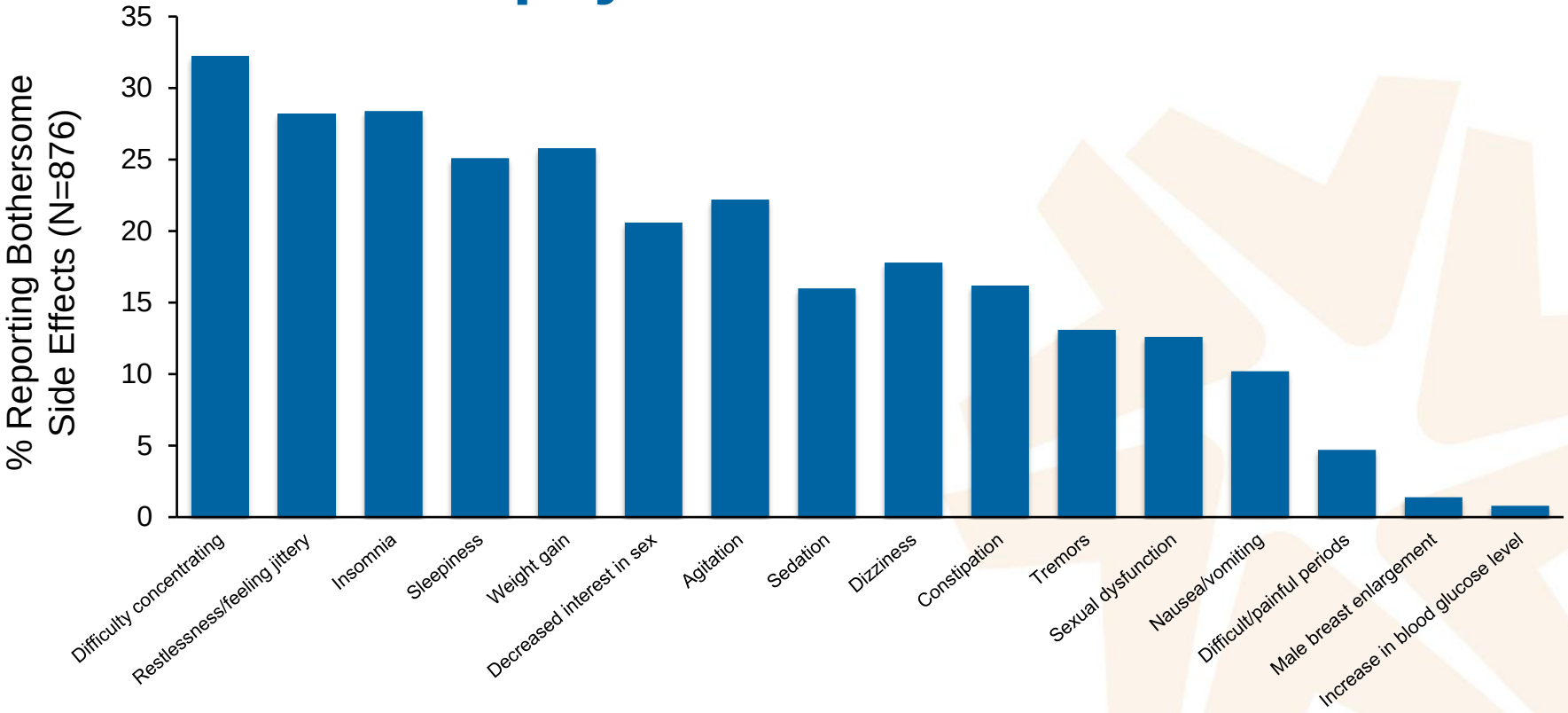
Increased All-cause and Specific-cause Mortality in Patients With Schizophrenia vs the General Population



CI=confidence interval.

Correll CU, et al. *World Psychiatry*. 2022;21:248–271.

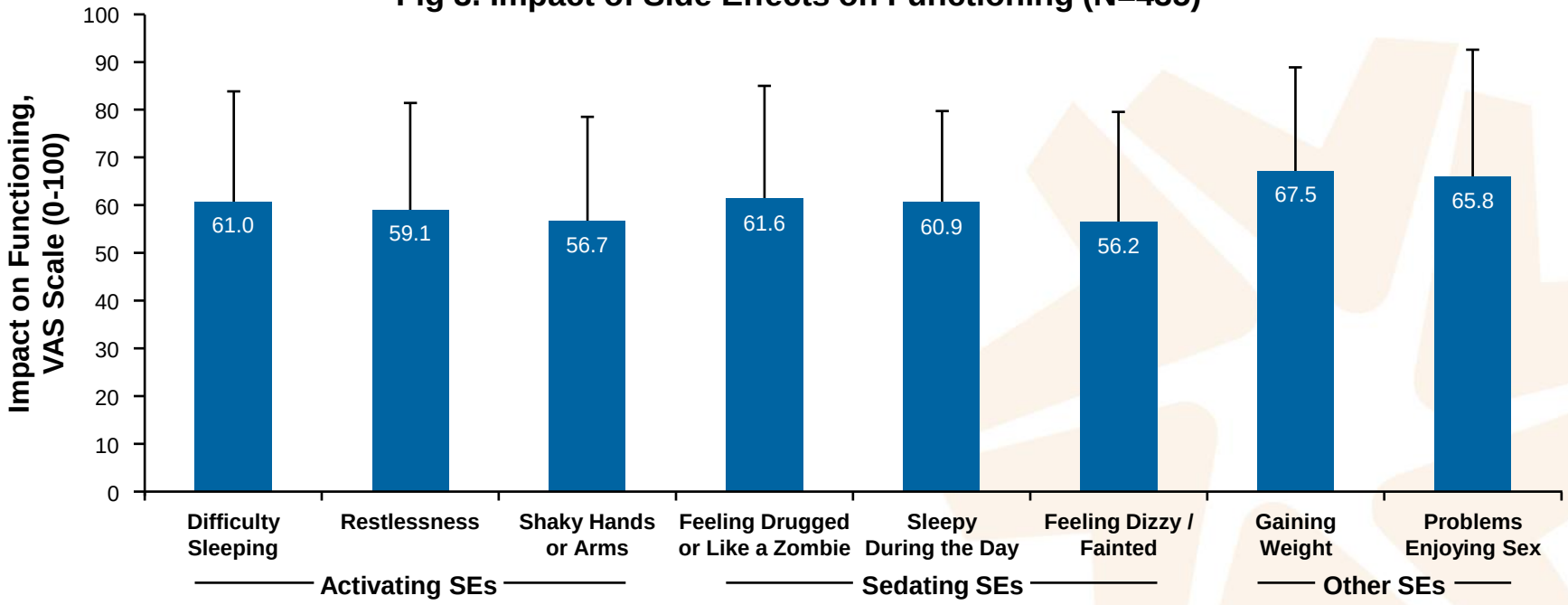
Patient Perspective of the Pervasiveness of Antipsychotic Side Effects



DiBonaventura M, et al. *BMC Psychiatry*. 2012;12:20.

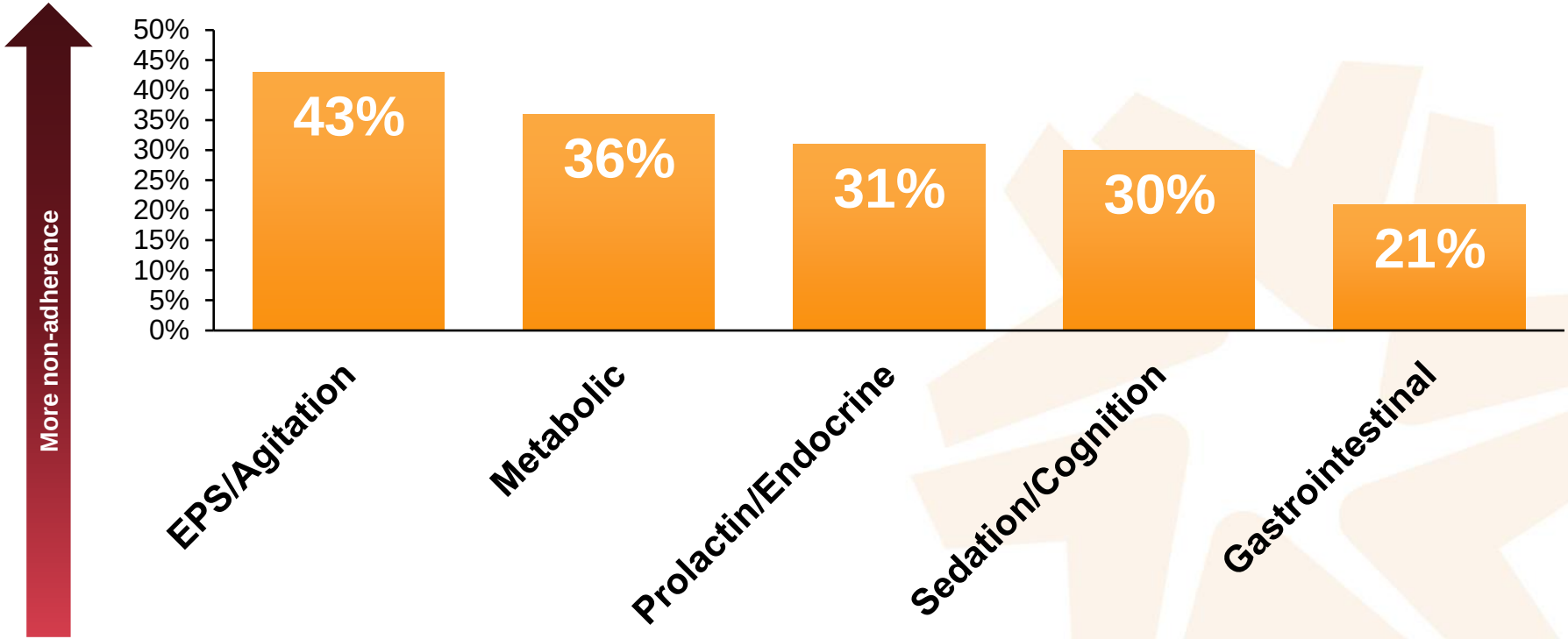
Adverse Effects and their Impact on Functioning: Patient Perspectives

Fig 3. Impact of Side Effects on Functioning (N=435)



VAS = Visual Analog Scale. Subset analysis based on whether key side effect is reported on the GASS scale.
* Higher functional severity indicates worse impact.
Tandon R, et al., Ann Gen Psychiatry. 2020 Jul 13;19:42.

Off-Target Adverse Effects and Poor Adherence



EPS=extrapyramidal symptoms.

DiBonaventura M, et al. *BMC Psychiatry*. 2012;12:20.

Key Learning Point

Antipsychotic efficacy has hardly improved while tolerability has only somewhat improved

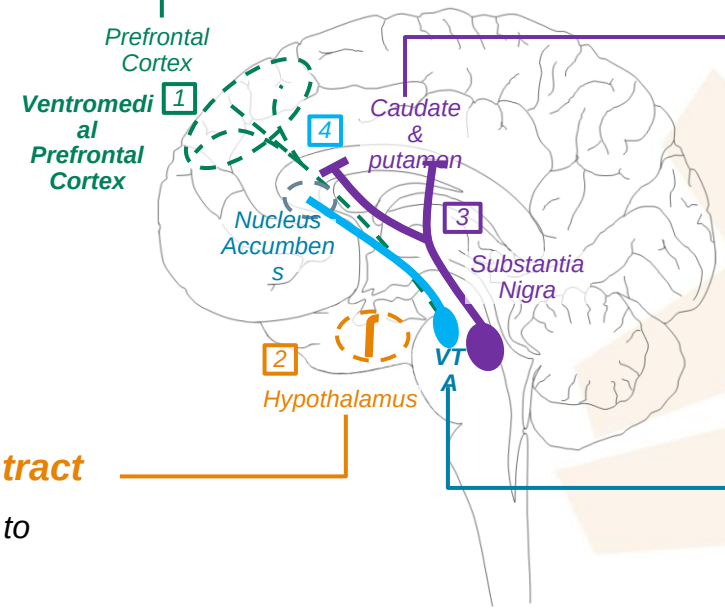
Pathophysiology of Schizophrenia

Christoph U Correll, MD

Where Psychosis Occurs: The ‘Mesolimbic’ Hypothesis

Mesocortical tract

- *DLPFC: cognitive and executive function*
- *VMPFC: implicated in negative and mood symptoms*



Nigrostriatal tract

- *Predominantly motor control*

Hypothalamohypophyseal tract

- *Dopamine acts at D_2 receptors to inhibits prolactin release*

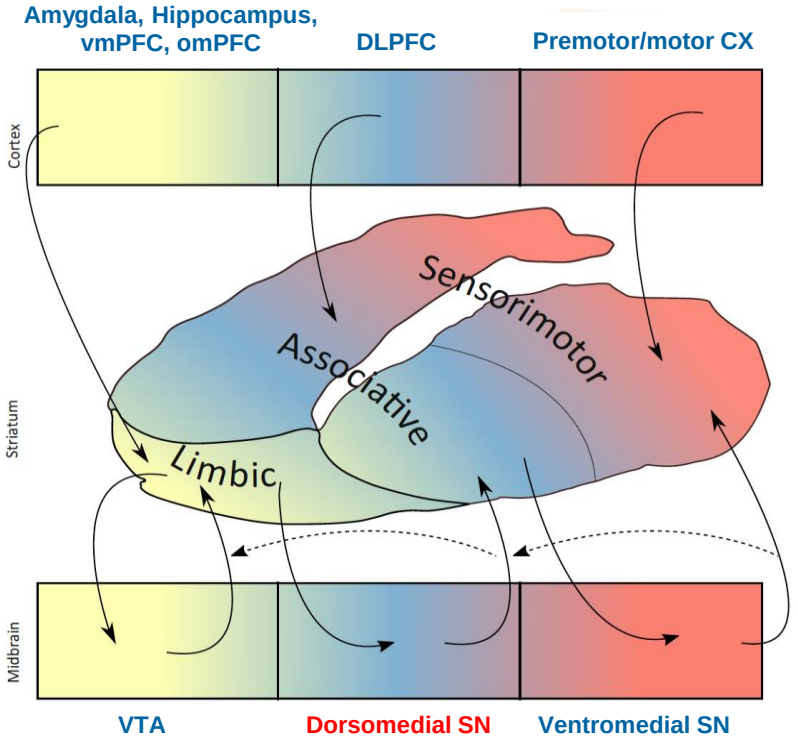
***Mesolimbic tract** (ventral tegmental area (VTA) → ventral striatum)*

- *Positive symptoms*

Brunelin J, et al. *Curr Med Chem*. 2013;20:397-404. Peuskens L, et al. *CNS Drugs.* 2014;28:421-453. Kondej M, et al. *IJMS.* 2018;19:3105. doi: 10.3390/ijms19103105. McCutcheon RA, et al. *Trends Neurosci*. 2019;42(3):205-220.

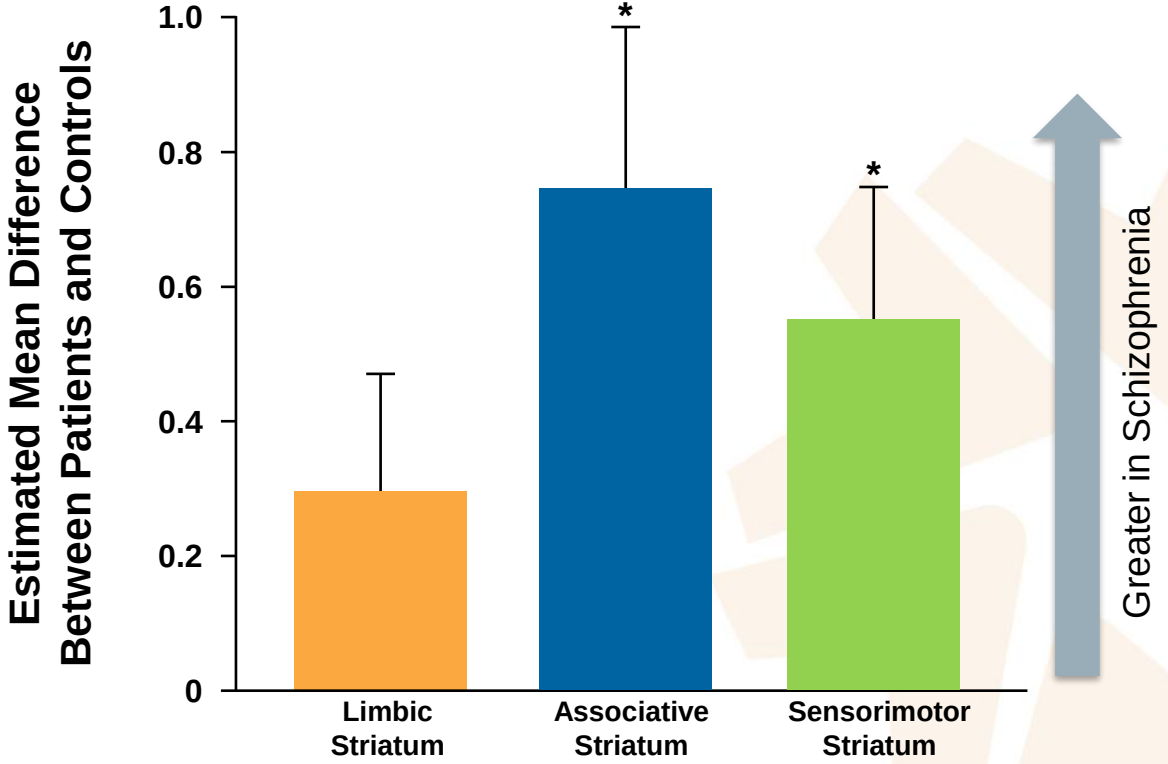
The Modern View of the Functional Organization of the Striatum

1. Improved resolution with PET imaging allowed in vivo human studies to accurately differentiate the organization of the striatum.
2. This 3 compartment model recognizes the associative striatum as a hub integrating cortical and subcortical inputs.
3. In human, dopamine overactivity in the ‘mesolimbic’ pathway from the VTA to the ventral striatum is not involved in the positive symptoms of psychosis
4. It is dopamine overactivity in the **SNASM**, the circuit from the dorsomedial substantia nigra (SN) to the associative and adjacent sensorimotor striatum (ASM), that is associated with the positive symptoms of schizophrenia



McCutcheon RA, et al. *Trends Neurosci*. 2019;42(3):205-220.

The Primary Dopamine Dysfunction of Schizophrenia
*Is in the **SNASM**, Not in the Mesolimbic Pathway*



***Statistically significant difference between patients and controls (*P*<.05 in a random effects meta-analysis).**

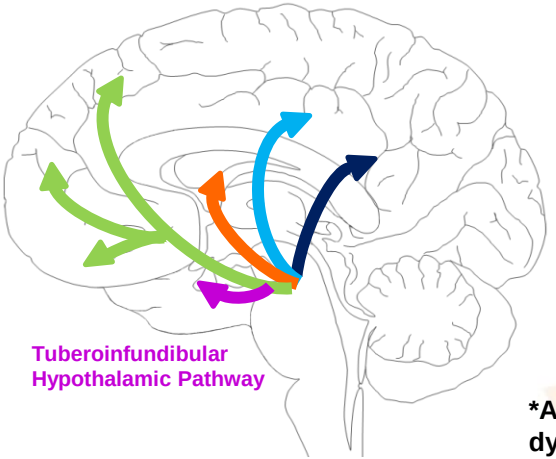
McCutcheon RA, et al. Dopamine and the Striatum: From Biology to Symptoms. *Trends Neurosci*. 2019 Mar;42(3):205-220. doi: 10.1016/j.tins.2018.12.004. Epub 2019 Jan 6. PMID: 30621912; PMCID: PMC6401206.

Disruptions of DA Pathways in Schizophrenia Lead to Changes in other Circuits[1,2]

Mesolimbic Pathway*
(Limbic Striatum)
- Negative symptoms

Nigrostriatal Pathway 1
(Associative Striatum)
- Psychosis

Mesocortical Pathway
- Negative symptoms
- Cognitive symptoms
- Depression



Nigrostriatal Pathway 2
(Sensorimotor Striatum)
- Dystonia
- Akinesia
- Rigidity
- Tremor
- Dyskinesia

Tuberoinfundibular Hypothalamic Pathway

- Negative symptoms: **underactivity** in the **mesolimbic** and **mesocortical** pathways
- Cognitive dysfunction: **underactivity** in the **mesocortical** pathway
- Positive symptoms: **overactivity** in the **nigrostriatal** pathway 1

***Advances in neuroimaging techniques found that DA dysfunction in schizophrenia is highest within nigrostriatal pathways, indicating the dorsal striatum is involved in the illness. DA overactivity in the circuit from the dorsomedial substantia nigra to the associative and adjacent sensorimotor striatum is linked to positive symptoms.[2]**

DA=dopamine.

1. Correll CU, et al. *J Clin Psychiatry.* 2022;83(1):SU21204IP1.
2. McCutcheon RA, et al. *Trends Neurosci*. 2019;42(3):205–220.

Effect of D2 Receptor Blockade on Neural Circuits[1,2]

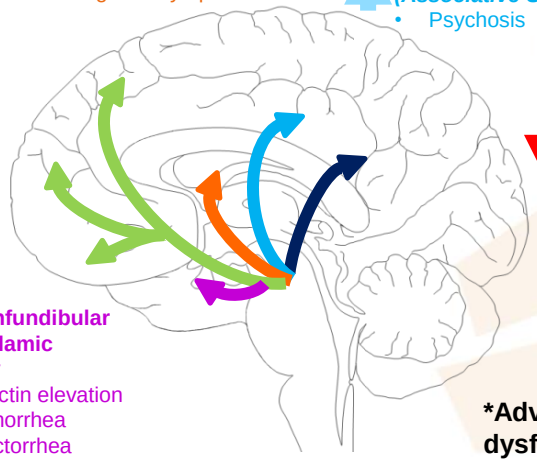
Underactivity of these circuits is associated with schizophrenia; the goal is to increase the activity

Overactivity of this circuit is associated with schizophrenia; the goal is to reduce the hyperactivity

Mesolimbic Pathway* ***(Limbic Striatum)***
- Negative symptoms

Nigrostriatal Pathway ***(Associative Striatum)***
- Psychosis

Mesocortical Pathway
- Negative symptoms
- Cognitive symptoms
- Depression



Nigrostriatal Pathway ***(Sensorimotor Striatum)***
- Dystonia
- Akinesia
- Rigidity
- Tremor
- Dyskinesia

Tuberoinfundibular Hypothalamic Pathway
- Prolactin elevation
- Amenorrhea
- Galactorrhea
- Sexual dysfunction

***Advances in neuroimaging techniques found that DA dysfunction in schizophrenia is highest within nigrostriatal pathways, indicating the dorsal striatum is involved in the illness. DA overactivity in the circuit from the dorsomedial substantia nigra to the associative and adjacent sensorimotor striatum is linked to positive symptoms.[2]**

DA=dopamine.

1. Correll CU et al. *J Clin Psychiatry.* 2022;83(1):SU21204IP1.
2. McCutcheon RA et al. *Trends Neurosci*. 2019;42(3):205–220.

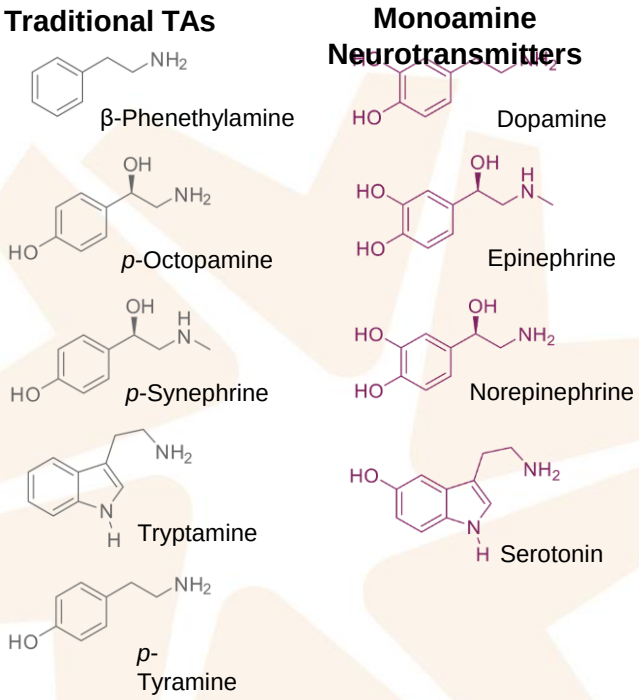
Evolving Treatment Landscape:

Trace-Amine Associated Receptors

What Are Trace Amines and TAARs?

- **Trace amines** (TAs):[1-4]
  - Endogenous chemical messengers, referred to as ”false neurotransmitters” because they are not released from synaptic vesicles when the neuron fires
    - Serve as true neurotransmitters in invertebrates
  - Structurally similar to monoamine neurotransmitters, eg, dopamine, norepinephrine, serotonin
    - Expressed at levels at least 100-fold lower than corresponding neurotransmitters[2]
    - Present in food (significant amounts in seafood, cured meats, wine, cheese, and chocolate)
    - Produced by human microbiota

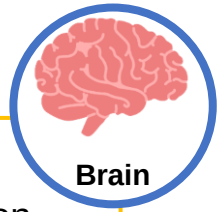
- **Trace amine-associated receptors** (TAARs):[1]
  - In 2001, TAs were found to selectively activate a family of receptors called TAARs.[1]
    - TAARs are predominantly intracellular receptors that modulate neurotransmission of dopamine, serotonin and glutamate.
    - Most studied is TAAR1



Adapted from Dedic N, et al.

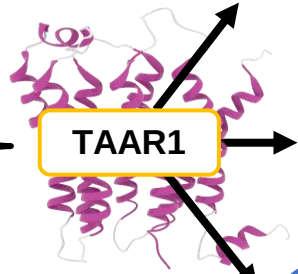
1. Nair PC, et al. *Mol Psychiatry*. 2022;27(1):88-94. 2. Gainetdinov RR, et al. *Pharmacol Rev*. 2018;70(3):549-620. 3. Dedic N, et al. *Int J Mol Sci*. 2021;22(24):13185. 4. Dodd S, et al. *Neurosci Biobehav Rev*. 2021;120:537-541.

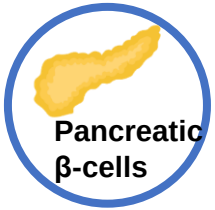
TAAR1 is Expressed in the Brain and Peripheral Tissues[1-3]

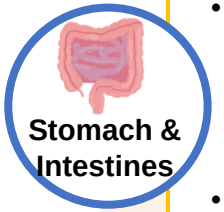


Brain

- In rodent brains, expression has been reported in the ventral tegmental area**,** substantia nigra**,** dorsal raphe nucleus**,** amygdala, basal ganglia, and prefrontal cortex





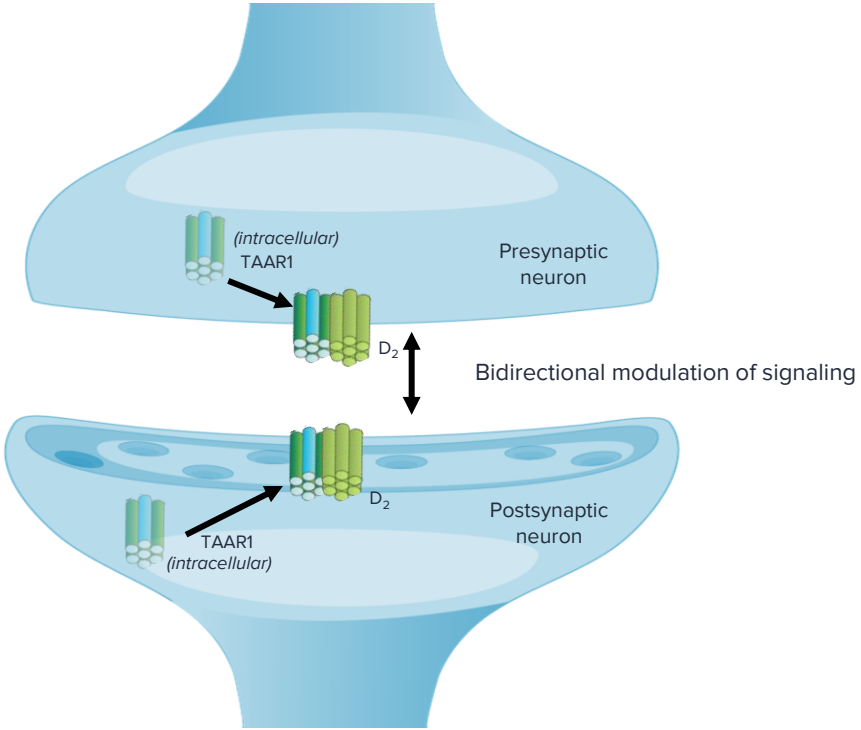


Periphery

- Localized in the gut and tissues associated with energy metabolism
- Highest expression outside of the CNS is in **pancreatic β-cells, stomach and intestines,** and **leukocytes**
- Preclinical evidence for potential utility in regulating glycemic control, immune response, fasting glucose, metabolic syndrome, and obesity[1-3]

Adapted from: Dodd S, et al. *Neurosci Biobehav Rev*. 2021;120:537-541.
1. Dedic N, et al. *Int J Mol Sci*. 2021;22(24):13185. 2. Nair PC, et al. *Mol Psychiatry*. 2022;27(1):88-94. 3. Dodd S, et al. *Neurosci Biobehav Rev*. 2021;120:537-541.

Cellular Localization of TAAR1



- **Predominantly intracellular** location, but **can move to the cell membrane** (and back into the cell)
- Can be found in both **pre-** and **postsynaptic neurons**
- Can form heterodimers with other receptors
  - For example, can interact with D_2 receptors presynaptically and postsynaptically to affect dopamine signaling and promote preferential inhibitory signaling

Adapted from: Gainetdinov RR, et al. *Pharmacol Rev*. 2018;70(3):549-620; and Berry MD, et al. *Pharmacol Ther.* 2017;180:161-180.

Investigational TAAR1 Agonists in Clinical Trials

Ralmitaront
(RO6889450)

TAAR1 partial agonist

- One active Phase 2 study in patients ages 18-55 with schizophrenia or schizoaffective disorder and negative symptoms[1]
  - Currently recruiting, with estimated completion May 2023
- One Phase 2 study recently terminated
  - In a preliminary analysis, the primary endpoint was negative[2]

Ulotaront
(SEP-363856)

TAAR1 agonist with 5-HT_{1A} agonist activity

- No affinity to dopamine D_2 or serotonin 5-HT_{2A} receptors
- In Phase 3 clinical development for the treatment of schizophrenia in patients ages 13-65
- Phase 2 studies complete in patients ages 18-40 with schizophrenia, resulting in FDA Breakthrough Therapy designation for treatment of schizophrenia
- Phase 1 studies currently evaluating effects of ulotaront on glucose and insulin parameters,[3] gastric emptying,[4] and weight-associated parameters[5]

1. ClinicalTrials.gov. Identifier: NCT03669640. 2. ClinicalTrials.gov. Identifier: NCT04512066. 3. ClinicalTrials.gov. Identifier: NCT05463770. 4. ClinicalTrials.gov. Identifier: NCT05402111. 5. ClinicalTrials.gov. Identifier: NCT05542264. All accessed August 22, 2023.

Ulotaront Phase 2B Study: Changes From Baseline in Efficacy Measures at Week (MMRM, ITT Population)

Efficacy Measure	Least-Squares Mean Change from Baseline at Week 4		Least-Squares Mean Difference (95% CI)
	SEP-363856, 50 mg or 75 mg	Placebo	
Primary end point			
PANSS total score	-17.2 ± 1.7	-9.7 ± 1.6	-7.5 (-11.9 to -3.0)†
Secondary end points‡			
CGI-S score	-1.0 ± 0.1	-0.5 ± 0.1	-0.5 (-0.7 to -0.2)
PANSS positive subscale score	-5.5 ± 0.5	-3.9 ± 0.5	-1.7 (-3.1 to -0.3)
PANSS negative subscale score	-3.1 ± 0.4	-1.6 ± 0.4	-1.5 (-2.6 to -0.4)
PANSS general psychopathology subscale score	-9.0 ± 0.9	-4.7 ± 0.8	-4.3 (-6.6 to -2.0)
BNSS total score	-7.1 ± 1.0	-2.7 ± 0.9	-4.3 (-6.8 to -1.8
MADRS total score	-3.3 ± 0.6	-1.6 ± 0.6	-1.8 (-3.2 to -0.3)

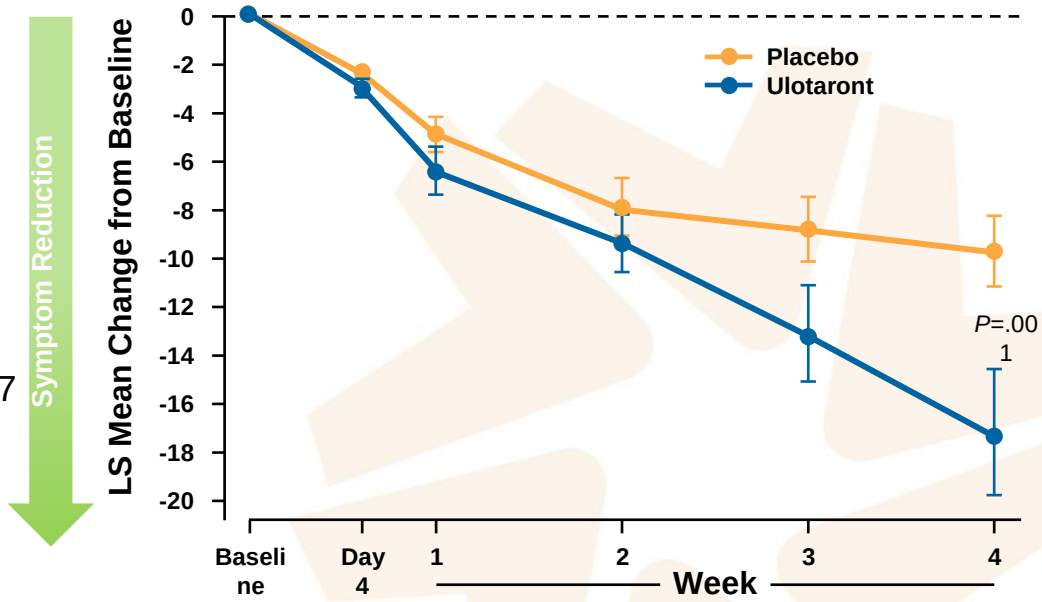
Koblan KS et al. N Engl J Med. 2020 Apr 16;382(16):1497-1506.

Ulotaront Phase 2B Data:
Efficacy Based on PANSS Total Score

PANSS Total Score:
Ulotaront: 17.2 ± 1.7 pts
Placebo: 9.7 ± 1.6 pts
(*P*=0.001; Effect size: 0.45)

Subscale Efficacy
PANSS Positive Subscale: p = 0.019, ES=0.32
PANSS Negative Subscale: p = 0.008, ES=0.37
PANSS General Psychopathology : p< 0.001, ES=0.51

≥20% Response Rate:
64.6% Ulotaront vs 44.0% PBO; NNT = 5



No. of Patients						
Placebo	125	125	122	117	113	100
Ulotaront	120	120	115	109	102	96

ES=Effect size
Koblan KS, et al. *N Engl J Med*. 2020;382(16):1497-1506.

Ulotaront Phase 2 Data: Tolerability in 4-week trial

Endpoint dose: 72.5% on 75 mg
Only 4/120 patients required dose reduction to 50 mg

78% on ulotaront and 79% on PBO completed study

Discontinuation due to AE: ulotaront=8.3%, PBO=6.4%;
NNH = 52 (ns)

Movement disorders[a]: Ulotaront = 3.3%, PBO = 3.2%

Treatment resulted in minimal changes in weight, lipids, and glycemic measures

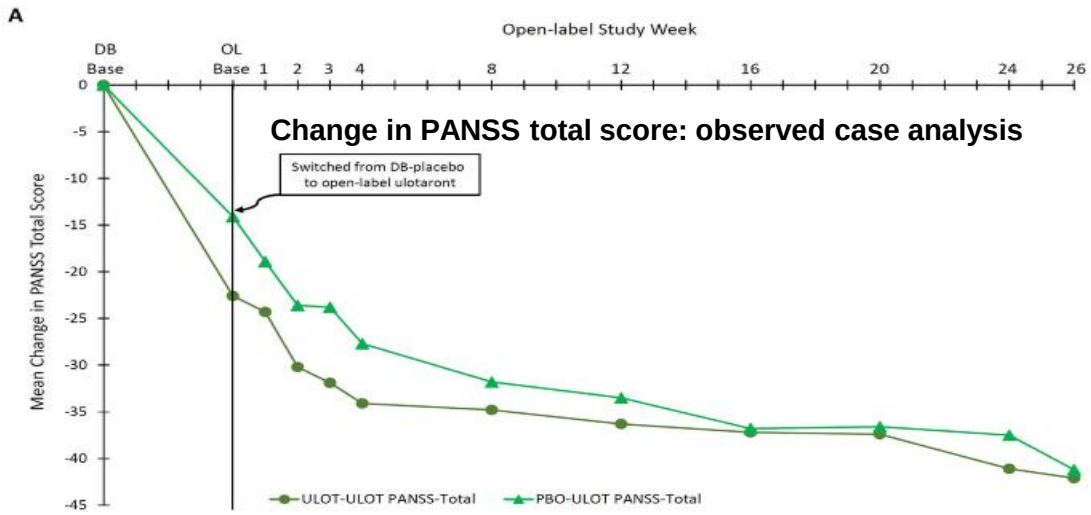
Effect on prolactin levels was minimal, comparable to placebo

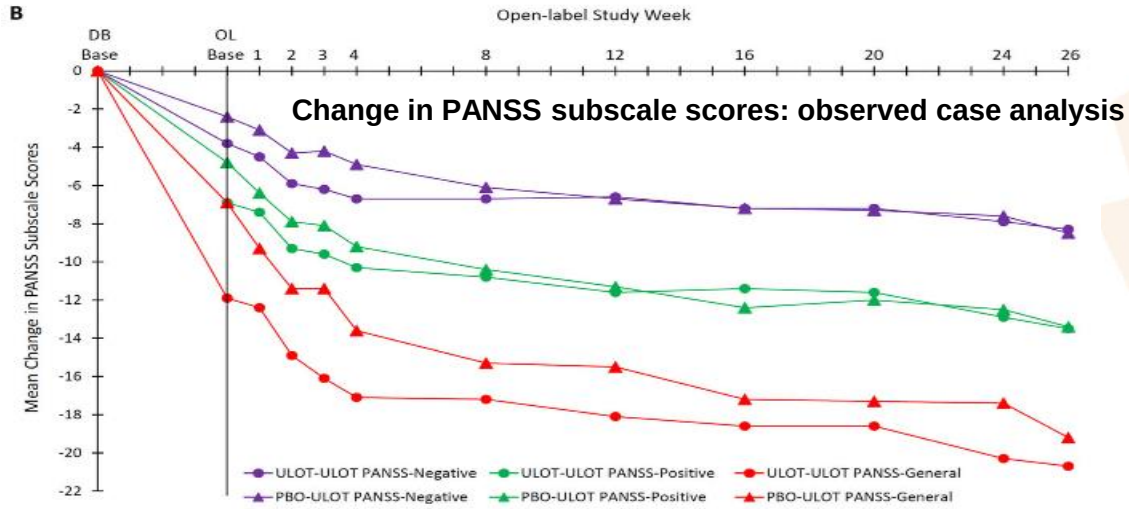
AEs ≥ 2% on ulotaront, > placebo	Ulotaront 50 mg or 75 mg	Placebo
Adverse events – no.		
Any adverse event	55 (45.8%)	63 (50.4%)
Somnolence	8 (6.7%)	6 (4.8)
Agitation	6 (5.0%)	6 (4.8)
Nausea	6 (5.0%)	4 (3.2)
Diarrhea	3 (2.5%)	1 (0.8)
Dyspepsia	3 (2.5%)	0
Serious adverse events – no./total no.		
Worsening of schizophrenia	1 (0.8%)	3 (2.4%)
Sudden cardiac death	1 (0.8%)	0
Suicide attempt	0	1 (0.8%)
Changes from baseline in body weight and BMI at week 4		
Body weight – lb	0.66 ± 4.2	-0.22 ± 5.1
Body mass index	0.1 ± 0.6	0.0 ± 0.8
Median changes from baseline in fasting metabolic labs at week 4		
Total cholesterol – mmol/liter	-0.2	0.0
LDL cholesterol – mmol/liter	-0.1	0.0
Triglycerides – mmol/liter	0.0	-0.1
Glucose – mmol/liter	0.0	0.1
Glycated hemoglobin – %	0.0	0.0
Median change from baseline in prolactin level at week 4		
male/female – mmol/liter	-0.037 / -0.175	-0.036 / -0.101

[a] akathisia, restlessness, musculoskeletal or joint stiffness, tremor, and nuchal rigi

CAD=coronary artery disease; HTN=hypertension; PE=pulmonary embolus.

Koblan KS, et al. *N Engl J Med*. 2020;382(16):1497-1506.





Mean Change from Baseline to 4-Week Double-Blind Treatment with Ulotaront (50,75 mg/d) or Placebo Followed by 26-wk Open-label Treatment with Flexibly Dosed Ulotaront (25, 50, 75 mg/d; n=156)

Correll CU, et al. *NPJ Schizophr.* 2021 Dec 9;7(1):63.

26-wk Open-label Tolerability and Safety Study of Flexibly Dosed Ulotaront (25, 50, 75 mg/d) in Patients with Schizophrenia (n=156)

Safety Parameter, n (%)	OL-ulotaront[a] (N=156)
Schizophrenia	19 (12.2)
Headache	18 (11.5)
Insomnia	13 (8.3)
Anxiety	8 (5.1)
Somnolence	7 (4.5)
Nasopharyngitis	7 (4.5)
Nausea	6 (3.8)
Irritability	5 (3.2)
Influenza	5 (3.2)
Weight decreased	5 (3.2)
Prolactin increased	4 (2.6)
Extrapyramidal adverse events, any Parkinsonism Dyskinesia Tremor Restlessness	5 (3.2) 2 (1.3) 1 (0.6) 1 (0.6) 1 (0.6)
At least one adverse event	88 (56.4)
Adverse events rated as “severe”	8 (5.1)

Safety Parameter	Double-blind Baseline		Week 26	
	N	Ulotaront	N	Ulotaront
Weight, kg, mean (SD)	156	75.4 (13.9)	104	-0.3 (3.7)
Body mass index, kg/m^2, mean (SD)	156	25.1 (3.9)	104	-0.1 (1.2)
Total cholesterol, mg/dL, median	156	174.5	111	-2.0
LDL cholesterol, mg/dL, median	156	101.5	111	-9.0
HDL cholesterol, mg/dL, median	156	48.0	111	0.0
Triglycerides, mg/dL, median	156	101.0	111	-5.0
Glucose, mg/dL, median	156	92.0	109	+2.0
HbA1c, %, median	155	5.2	109	0.0
Prolactin, ng/dL, median Female Male	 54 102	 16.1 11.6	 39 73	 -3.4 -2.7

Lipid and glucose data are shown for total available patients at week 26; 96.4% (107/111) of lipid results were fasted at week 26, 96.3% (105/109) of glucose results were fasted at week 26.
Ulotaront data are shown for all extension phase patients; mean baseline and change values are shown for weight and BMI; median baseline and change values are shown for laboratory parameters.

[a]All extension phase patients.
OL = open-label; HDL = high-density lipoprotein; LDL = low-density lipoprotein.
Correll CU, et al. NPJ Schizophr. 2021 Dec 9;7(1):63.

Ulotaront Phase 3 DIAMOND 1 and 2 Trials: Top Line Results

- DIAMOND 1 study: multicenter, randomized, double-blind, parallel-group, fixed-dosed trial comparing **ulotaront 50 mg/d and 75 mg/d vs placebo** over 6 weeks in 435 acutely psychotic adults with schizophrenia.

- All three groups showed a reduction in the Positive and Negative Syndrome Scale (PANSS) total score over time, without either ulotaront treatment group being superior to placebo on PANSS total change at Week 6 (least squares [LS] mean:
  - **ulotaront 50 mg/day: -16.9; ulotaront 75 mg/day: -19.6; placebo: -19.3 points**

- DIAMOND 2 study: multicenter, randomized, double-blind, parallel-group, fixed-dosed trial comparing **ulotaront 75 mg/d and 100 mg/d vs. placebo over 6 weeks** in 464 acutely psychotic adults with schizophrenia

- All three groups showed a reduction in PANSS total score over time, without either ulotaront treatment group being superior to placebo on PANSS total change at Week 6 (least squares [LS] mean:
  - **ulotaront 75 mg/day: -16.4; ulotaront 100 mg/day: -18.1; placebo: -14.3 points**

- Ulotaront was generally safe and well-tolerated in both studies.

Key Learning Points

- The TAAR-1 system is an exciting neuromodulatory system that is related to key metabolic and CNS functions
- TAAR-1 agonism has been shown to improve symptoms associated with an acute exacerbation of schizophrenia in a phase 2B study
- Results from two phase 3 trials (DIAMOND 1 and DIAMOND-2) were negative, however, suffering from a very high placebo effect

Key Learning Points (continued)

- Ulotaront was generally safe and well-tolerated in all 3 acute studies and a 6-month open-label extension study
- Additional data are needed to fully evaluate the potential of TAAR-1 modulation for schizophrenia and other mental disorders

Vesicular Monoamine Transporter-2 (VMAT-2) Inhibition

Brooke Kempf, PMHNP-BC

Dopamine and Acetylcholine Balance in the Dorsal Striatum

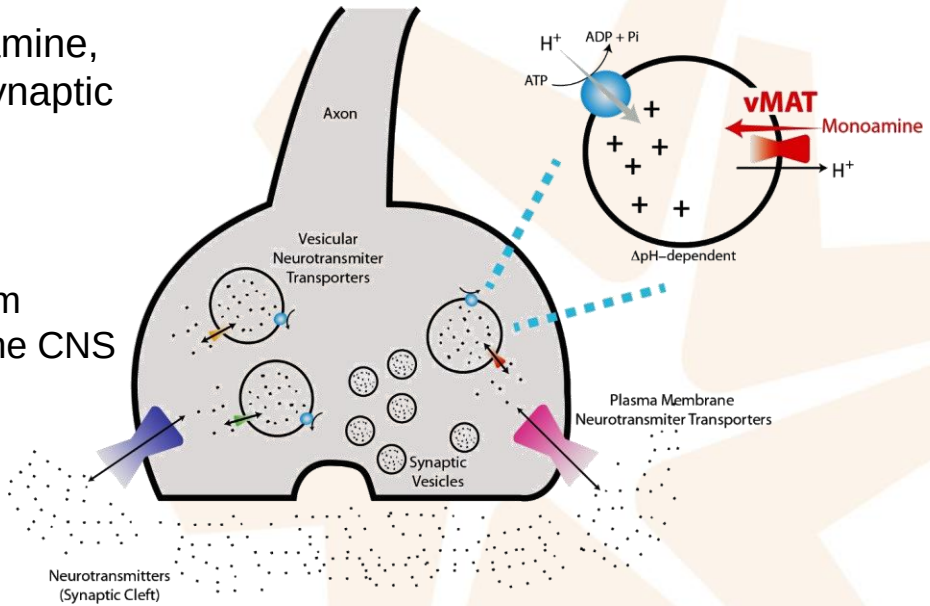
New Therapeutic Strategies for Schizophrenia??

McCutcheon RA et al. *Trends Neurosci.* 2019;42(3):205–220.

Vesicular Monoamine Transporter (VMAT)

VMAT is a protein concentrated in the human brain that is primarily responsible for
re-packaging and transporting monoamines (dopamine, norepinephrine, serotonin, and histamine) in pre-synaptic neurons

–VMAT1: expressed mainly in peripheral nervous system
–VMAT2: expressed mainly in monoaminergic cells of the CNS



Meyer JM. Forgotten but not gone: new developments in the understandingand treatment of tardive dyskinesia. *CNS Spectrums*. 2016; 21:13-24

VMAT Inhibitors

Reserpine

- 1940s began to be used as a treatment for people with mental disorders and was one of the very first antipsychotic drugs
- Depletes dopamine, norepinephrine and serotonin and represses vesicular formation of these in the brain
- Reserpine irreversibly binds itself to the vesicular amine transporter (long lasting side effects
- Reserpine and chlorpromazine had similar rates of adverse effects, but that reserpine was less effective than chlorpromazine for improving a person's global state in schizophrenia
- Doses in excess of 3 mg daily often required use of an anticholinergic drug to combat excessive cholinergic activity/ parkinsonism.
- For adjunctive treatment, doses are typically kept at or below 0.25 mg twice a day.

Tetrabenazine

- Developed in 1950's as an antipsychotic
- Reversible and selective VMAT2 inhibiton
- 2008 Approved for Huntington's Chorea
- Study indicated improvement in TD symptoms in up to 70% of patients
  - 54% reduction in symptoms (data mainly from observational studies)
- Disadvantages
  - Short half life (TID dosing)
  - Depression/ suicidality
  - Parkinsonism/akathisia
- Off label dosing for TD: 12.5 mg daily for one week and increased by 12.5 mg increments every few days, usual effective dose of 75 to 150 mg daily. Daily doses >37.5 mg should be divided into three doses. Requires CYP2D6 genotyping for doses >50mg

Deutetrabenazine

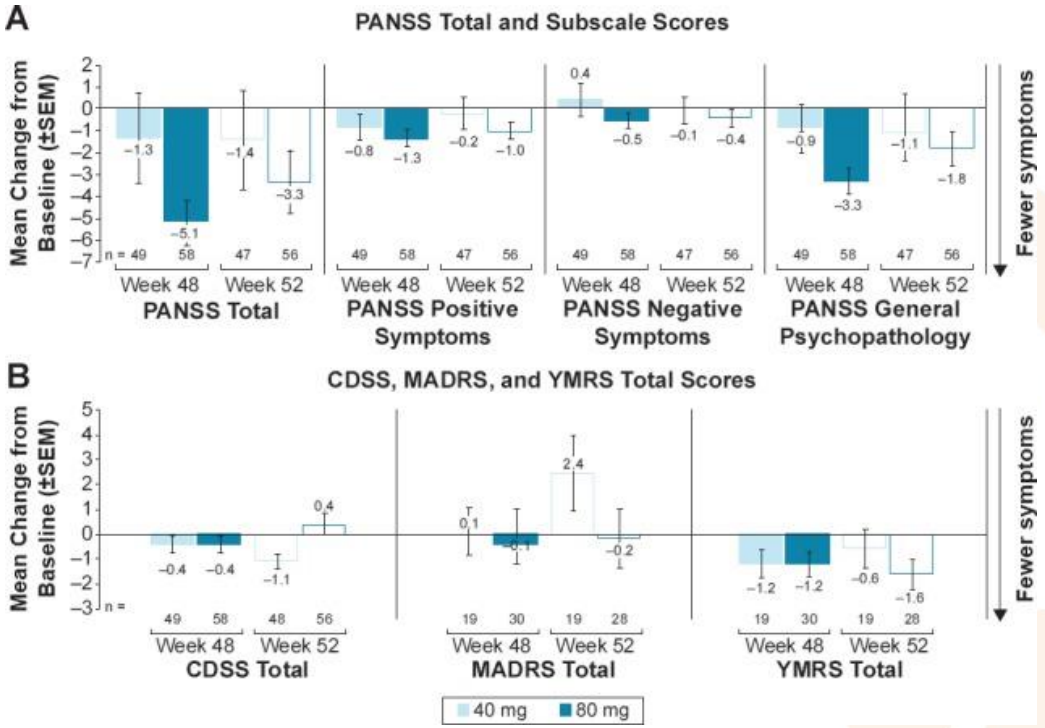
- 2017 approved for Huntington's related chorea and TD
- 2023 extended release approved
- Similar chemical structure to tetrabenazine but replaces hydrogen atoms with deuterium for 8 x stronger bond
  - Improved PK/prolongs half life
- Dose titration by 6mg in weekly increments ranging from 12-48mg daily

Valbenazine

- 2017 Approved for TD
- prodrug of an isomer of tetrabenazine
- Slowly metabolized into active metabolites highly selective for VMAT2/ low affinity for other receptors
  - Less PK variability
  - Allows once daily dosing
- 40 mg once daily; after 1 week, increase to 80 mg once daily.
  - 40 or 60 mg once daily may be considered for some patients based on response and tolerability

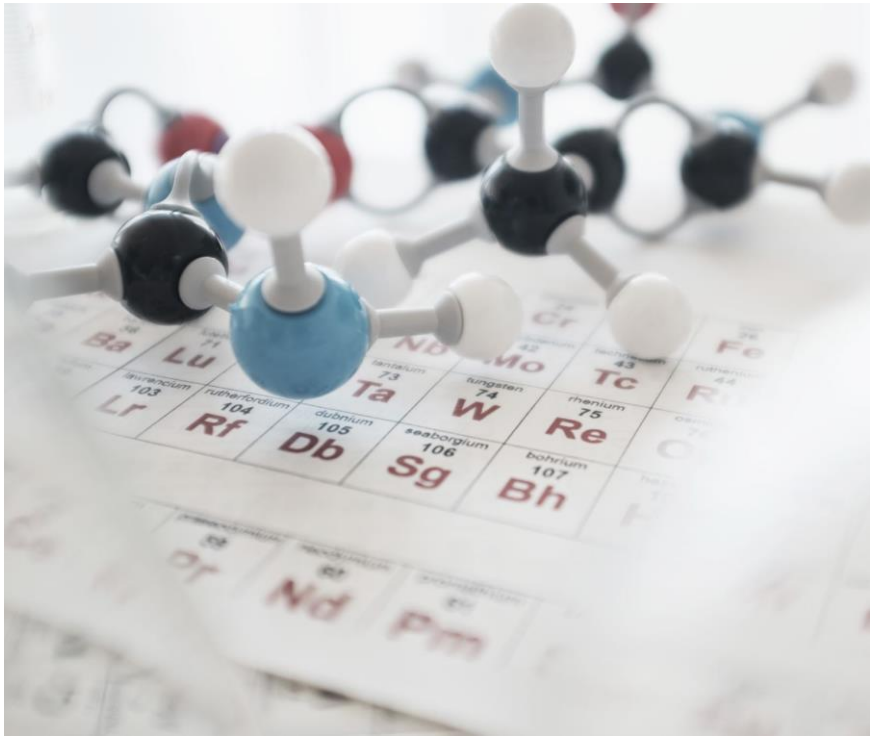
Nasrallah, H, et al. Psychiatrist's Role in Tardive Dyskinesia: From Diagnosis to Emerging Treatment. *Medscape*, 27 Jun. 1917, Accessed August 22, 2023. www.medscape.org/viewarticle/880292_transcript.. Nur S, et al. Chlorpromazine versus reserpine for schizophrenia. *Cochrane Database Syst Rev*. 2016;4(4):CD012122. Published 2016 Apr 28. doi:10.1002/14651858.CD012122.pub2

A Phase 3, 1-Year, Open-Label Trial of Valbenazine in Adults with Tardive Dyskinesia



Josiassen RC, Kane JM, Liang GS, Burke J, O'Brien CF. Long-Term Safety and Tolerability of Valbenazine (NBI-98854) in Subjects with Tardive Dyskinesia and a Diagnosis of Schizophrenia or Mood Disorder. *Psychopharmacol Bull*. 2017;47(3):61-68.

Journey Study: Evaluate the Efficacy, Safety, and Tolerability of Valbenazine as Adjunctive Treatment for Schizophrenia



- Phase 3, Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Valbenazine as Adjunctive Treatment in Subjects With Schizophrenia

- Primary Outcome Measures:
  - Change in Positive and Negative Syndrome Scale (PANSS) total score from baseline to Week 10 [Time Frame: Baseline to week 10]

- Secondary Outcome Measures :
  - Change in Clinical Global Impression of Severity (CGI-S) score from baseline to Week 10 [Time Frame: Baseline to week 10]
  - Change in Personal and Social Performance Scale (PSP) score from baseline to Week 10 [Time Frame: Baseline to week 10]

Estimated Study Completion Date: September 2024

Journey Study: Evaluate the Efficacy, Safety, and Tolerability of Valbenazine as Adjunctive Treatment for Schizophrenia. ClinicalTrials.gov identifier: NCT05110157. Accessed August 28, 2023. https://clinicaltrials.gov/study/NCT05110157

Key Learning Points

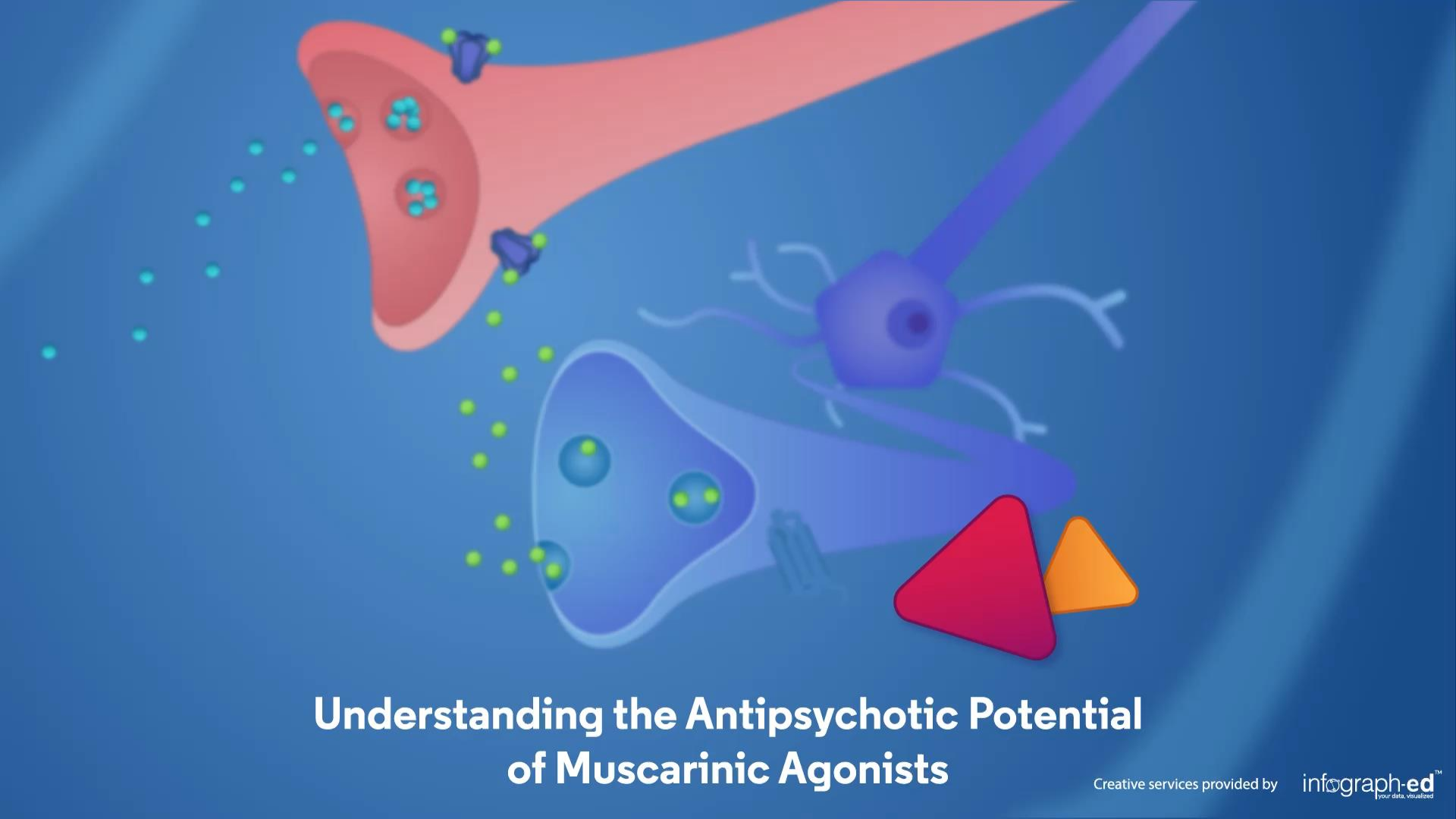
- VMAT-2 inhibitors **decrease presynaptic dopamine release**
- Presynaptic dopamine modulation may provide additional mechanism of action for symptoms of schizophrenia in addition to tardive dyskinesia
- Reserpine and tetrabenazine have previously been used for symptoms of schizophrenia, but the side effect profile and pharmacokinetic profiles limited use

Key Learning Points (continued)

- Current Phase 3 trial (Journey) Study to evaluate the efficacy, safety, and tolerability of **valbenazine** as adjunctive treatment for schizophrenia estimated to be completed in September 2024
- Additional data are needed to fully evaluate the potential of VMAT 2 inhibition for schizophrenia and other mental disorders

Evolving Treatment Landscape: M1/M4 Muscarinic Agonism

Christoph U Correll, MD

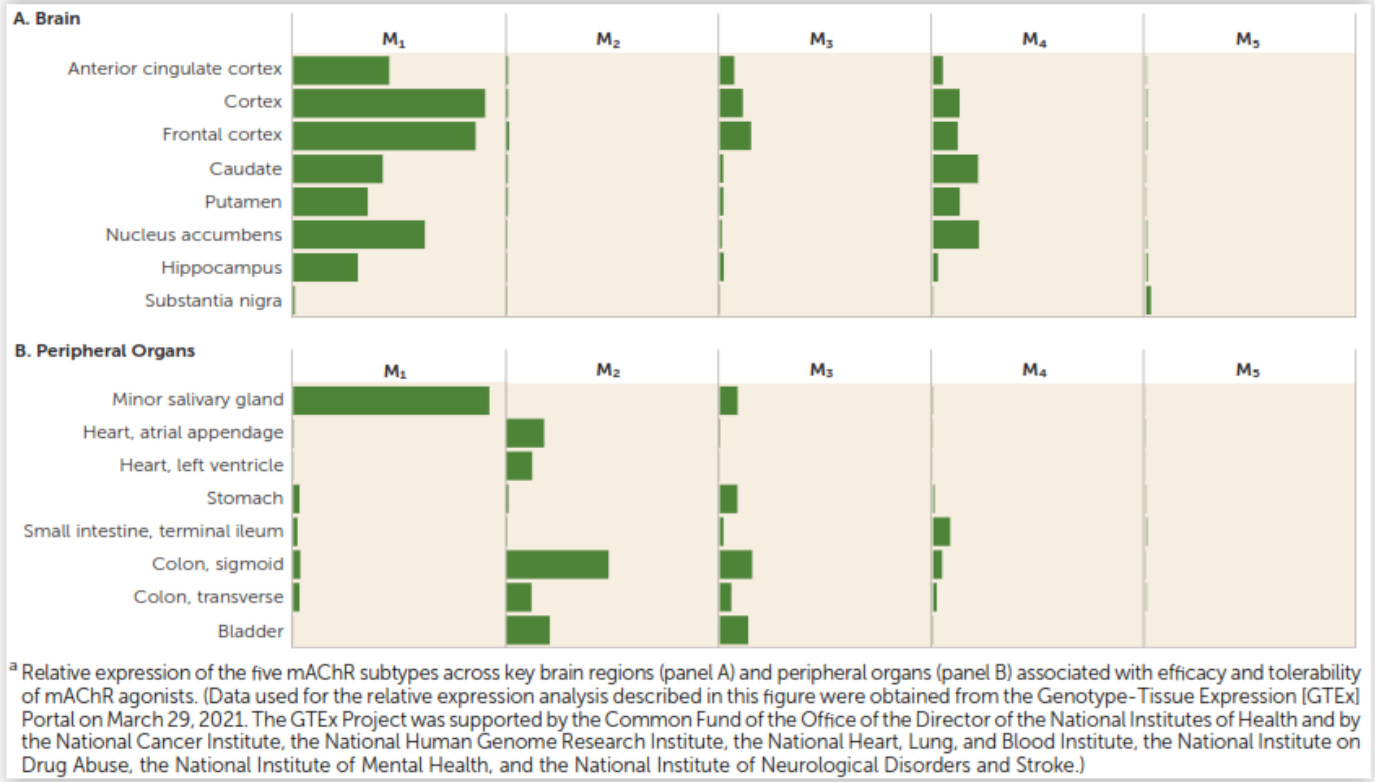


Understanding the Antipsychotic Potential of Muscarinic Agonists

Activation of M_4 Receptors in the Ventral Tegmental Area and Nucleus Accumbens

How M_1 Receptor Agonism Modulates Dopamine Release

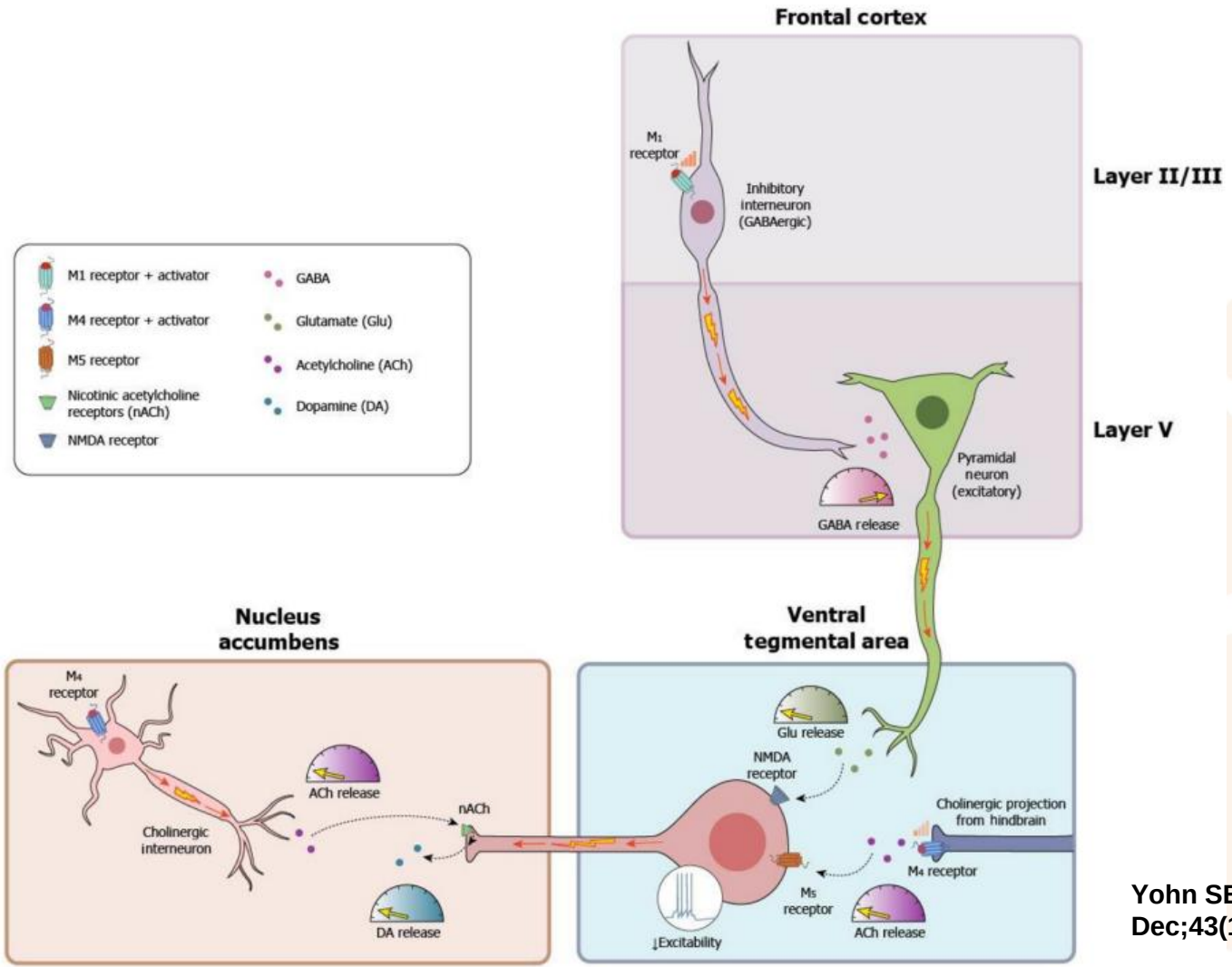
Quantification and Localization Muscarinic Acetylcholine Receptor (mAChR) mRNAs in Central and Peripheral Human Tissues Using RNA Sequencing



[a] Relative expression of the five mAChR subtypes across key brain regions (panel A) and peripheral organs (panel B) associated with efficacy and tolerability of mAChR agonists. (Data used for the relative expression analysis described in this figure were obtained from the Genotype-Tissue Expression [GTEx] Portal on March 29, 2021. The GTEx Project was supported by the Common Fund of the Office of the Director of the National Institutes of Health and by the National Cancer Institute, the National Human Genome Research Institute, the National Heart, Lung, and Blood Institute, the National Institute on Drug Abuse, the National Institute of Mental Health, and the National Institute of Neurological Disorders and Stroke.)

Paul SM, et al. *Am J Psychiatry*. 2022 Sep;179(9):611-627.

Regulation of Dopamine Circuits Relevant in Psychosis by M1 & M4 Receptors



Yohn SE, et al. *Trends Pharmacol Sci.* 2022 Dec;43(12):1098-1112.

Xanomeline + Trospium Chloride (KarXT) Phase 2B Study: Prespecified Primary and Secondary Endpoint Analysis (mITT)

Efficacy Measure†	Xanomeline-Trospium (N=83)	Placebo (N=87)	Difference (95% CI)	*P* Value
Primary and point				
Least-squares mean change from baseline in PANSS total score	-17.4 ± 1.8	-5.9 ± 1.7	-11.6 (-16.1 to -7.1)‡	<.001‡
Secondary and points§				
Least-squares mean change from baseline in PANSS positive symptom subscore	-5.6 ± 0.6	-2.4 ± 0.6	-3.2 (-4.8 to -1.7)	<.001
Score on the CGI-S scale (%)				<.001
1. Normal 2. Borderline ill 3. Mildly ill 4. Moderately ill 5. Markedly ill 6. Severely ill 7. Extremely ill	1 4 32 29 29 3 1	0 1 10 29 52 6 3	1 3 22 0 -23 -3 -1	
Least-squares mean change from baseline in PANSS negative symptom subscore	-3.2 ± 0.5	-0.9 ± 0.5	-2.3 (-3.5 to -1.1)	<.001
Least-squares mean change from baseline in PANSS Marder negative symptom subscore	-3.9 ± 0.5	-1.3 ± 0.5	-2.5 (-3.9 to -1.2)	<.001
Response according to CGI-S score of 1 or 2 (%)	6	1	4 (-3 to 12)	.15

Brannan SK. *N Engl J Med*. 2021 Feb 25;384(8):717-726.

Xanomeline + Trospium (KarXT) Phase 2B Study: Adverse Effects

Variable	Xanomeline-Trospium (N=89)	Placebo (N=90)
Any adverse event, no. (%)	48 (54)	39 (43)
Serious adverse event, no. (%)	1 (1)	0
Severe adverse event, no. (%)	1 (1)	1 (1)
Adverse event leading to discontinuation of the active drug or placebo, no. (%)	2 (2)	2 (2)
Adverse events occurring in ≥2% of the patients in the xanomeline-trospium group, no. (%)		
Constipation	15 (17)	3 (3)
Nausea	15 (17)	4 (4)
Dry Mouth	8 (9)	1 (1)
Dyspepsia	8 (9)	4 (4)
Vomiting	8 (9)	4 (4)
Headache	6 (7)	5 (6)
Somnolence	5 (6)	4 (4)
Akathisia	3 (3)	0
Dizziness	3 (3)	3 (3)
Increased weight	3 (3)	4 (4)
Tachycardia	3 (3)	2 (2)
Sedation	2 (2)	2 (2)
Diarrhea	2 (2)	4 (4)
Increased γ-glutamyltransferase level	2 (2)	0
Agitation	2 (2)	1 (1)
Insomnia	2 (2)	2 (2)
Decreased appetite	2 (2)	0
Hyperhidrosis	2 (2)	1 (1)
Mean change from baseline in body weight at wk 5, kg	1.5 ± 2.8	1.1 ± 3.5
Mean change from baseline in score on Simpson-Angus Scale at wk 5	-0.1 ± 0.7	-0.1 ± 0.8
Mean change from baseline in score on Barnes Akathisia Rating Scale at wk 5	-0.1 ± 1.0	0.0 ± 0.7

Brannan SK. *N Engl J Med*. 2021 Feb 25;384(8):717-726.

EMERGENT-1: Severity and Number-Needed-to-Harm (NNH) Estimates of Procholinergic and Anticholinergic Adverse Events (reported by ≥2% of patients in the KarXT group and at >2-fold higher incidence vs Placebo).

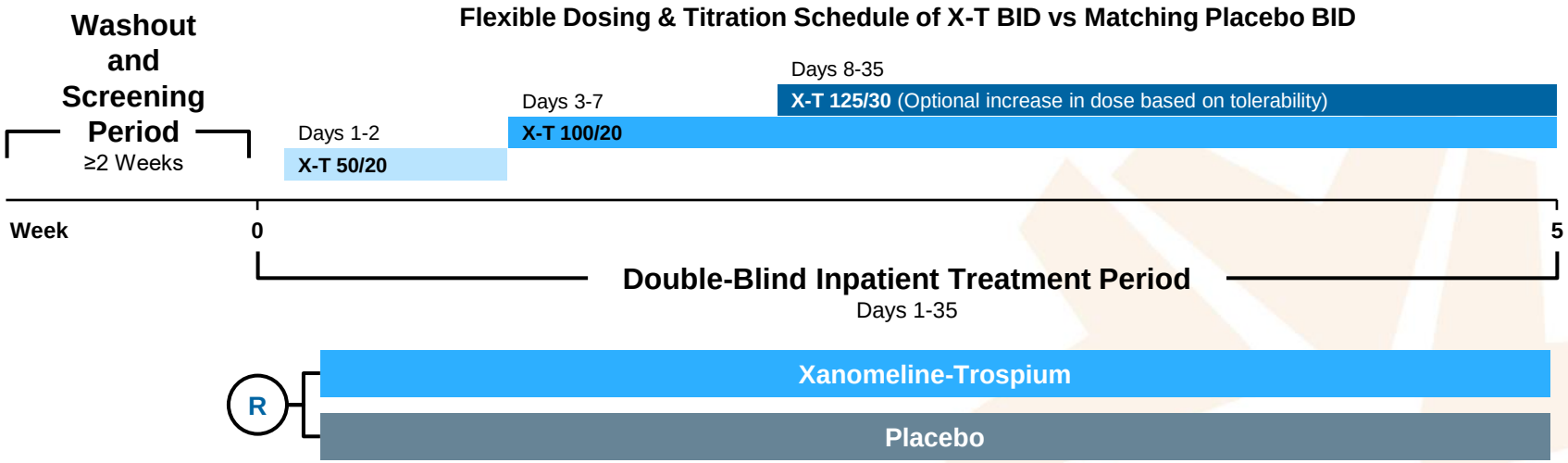
n/N (%)	KarXT (n=89)			Placebo (n=90)			NNH (95% CI)
	Mild	Moderate	Severe	Mild	Moderate	Severe	
Procholinergic AEs							
Nausea	13/15 (86.7)	2/15 (13.3)	0/15 (0)	3/4 (75.0)	1/4 (25.0)	0/4 (0)	9 (5, 29)
Vomiting	5/8 (62.5)	3/8 (37.5)	0/8 (0)	3/4 (75.0)	1/4 (25.0)	0/4 (0)	23 (9, -36)
Anticholinergic AEs							
Constipation	12/16 (75.0)	4/16 (25.0)	0/16 (0)	2/3 (66.7)	1/3 (33.3)	0/3 (0)	8 (5, 21)
Dry mouth	6/8 (75.0)	2/8 (25.0)	0/8 (0)	1/1 (100)	0/1 (0)	0/1 (0)	13 (8, 65)

The majority of procholinergic and anticholinergic AEs with KarXT were mild, occurred in the first 1-2 weeks of treatment, and were transient with a median duration ranging from 1 day for vomiting to 13 days for dry mouth. No patients in either treatment group discontinued the study due to any procholinergic or anticholinergic AEs.

AE = adverse event; CI = confidence interval; NNH = number needed to harm.

Correll CU, et al. Schizophrenia (Heidelb). 2022 Dec 3;8(1):109.

EMERGENT-2 Phase 3 Trial Design



Double-blind, placebo-controlled, 5-week phase 3 inpatient trial

Adults aged 18–**65** with an acute exacerbation of schizophrenia.

Mean age 45.6 years, 75% male, 77.4% nonwhite, mean baseline PANSS 98.1

Correll CU, et al. Poster Presented at Psych Congress 2022. September 17-20, 2022.

KarXT Phase EMERGENT-2 and EMERGENT-3: Baseline Characteristics

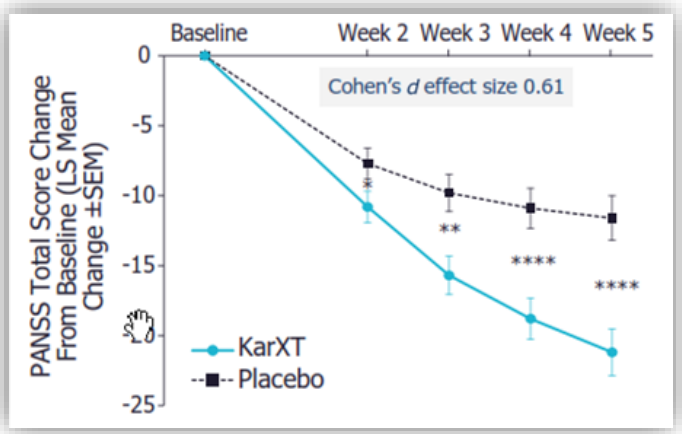
Table 1. Baseline Demographics and Characteristics (ITT Population)

Variable	EMERGENT-2		EMERGENT-3	
	KarXT (n=126)	Placebo (n=126)	KarXT (n=125)	Placebo (n=131)
Age, mean ± SD	45.6 ± 10.4	46.2 ± 10.8	43.6 ± 11.4	42.6 ± 12.2
Sex, n (%)				
Male Female	95 (75.4) 31 (24.6)	95 (75.4) 31 (24.6)	87 (69.6) 38 (30.4)	104 (79.4) 27 (20.6)
Race, n (%)				
Asian Black or African American Caucasian Other Not reported	2 (1.6) 97 (77.0) 26 (20.6) 1 (0.8) 0	1 (0.8) 92 (73.0) 31 (24.6) 2 (1.6) 0	1 (0.8) 79 (63.2) 45 (36.0) 0 0	0 77 (58.8) 53 (40.5) 0 1 (0.8)
Baseline PANSS total score, mean ± SD	98.3 ± 8.9	97.9 ± 9.7	97.3 ± 8.9	96.7 ± 8.9
Baseline PANSS positive subscale score, mean ± SD	26.8 ± 3.7	26.7 ± 4.0	26.9 ± 3.7	26.4 ± 3.3
Baseline PANSS negative subscale score, mean ± SD	22.9 ± 4.0	22.9 ± 3.8	22.6 ± 3.2	22.0 ± 3.7
Baseline PANSS Marder negative factor score, mean ± SD	22.9 ± 5.0	22.5 ± 4.7	22.0 ± 3.7	21.8 ± 4.2
Baseline CGI-S, mean ± SD	5.1 ± 0.6	5.1 ± 0.6	5.1 ± 0.7	5.0 ± 0.6

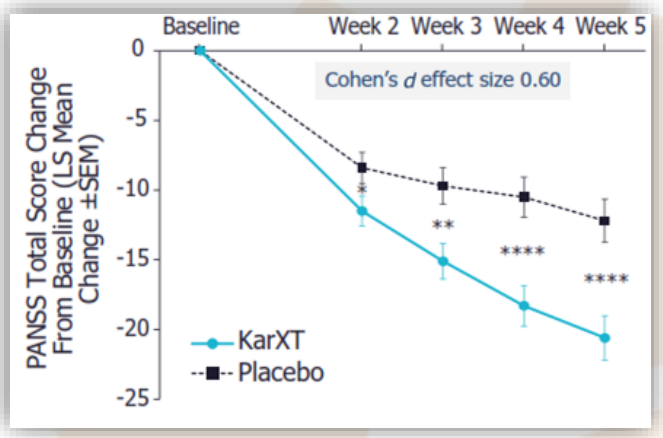
ITT defined as all randomized participants.
CGI-S = Clinical Global Impression-Severity; ITT = intent-to-treat; PANSS = Positive and Negative Syndrome Scale; SD = standard deviation. Brannan SK, et al. Poster presented at the 2023 American Society of Clinical Psychopharmacology (ASCP) Annual Meeting, May 30-June 2, 2023, Miami, Florida.

KarXT Phase EMERGENT-2 and EMERGENT-3: Change in Total PANSS from Baseline to Week 5

EMERGENT-2



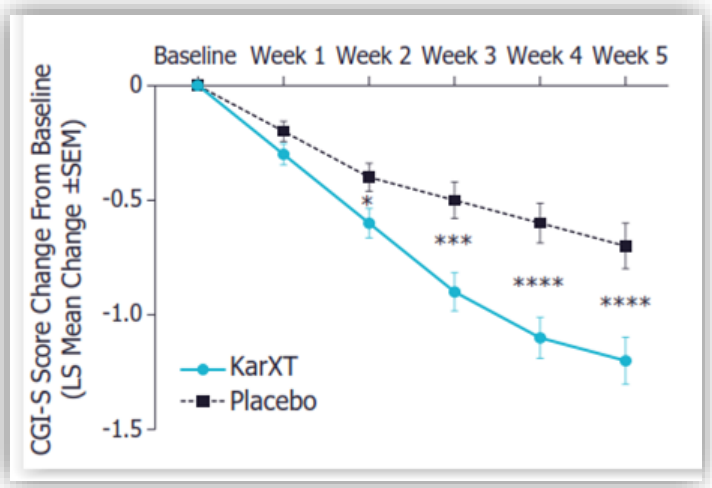
EMERGENT-3



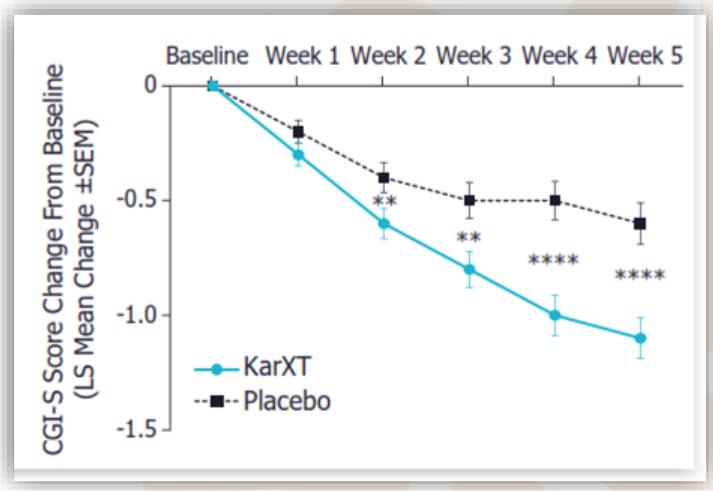
***P*<0.05; ****P*<0.01; *****P*<0.0001.
Efficacy analyses performed in modified intent-to-treat population.
LS = lease squares; PANSS = positive and negative syndrome scale; SEM = standard error of the mean
Brannan SK, et al. Poster presented at the 2023 American Society of Clinical Psychopharmacology (ASCP) Annual Meeting, May 30-June 2, 2023, Miami, Florida.

KarXT Phase EMERGENT-2 and EMERGENT-3: Change in Clinical Global Impressions-Severity Scale (CGI-S) From Baseline to Week 5

EMERGENT-2



EMERGENT-3



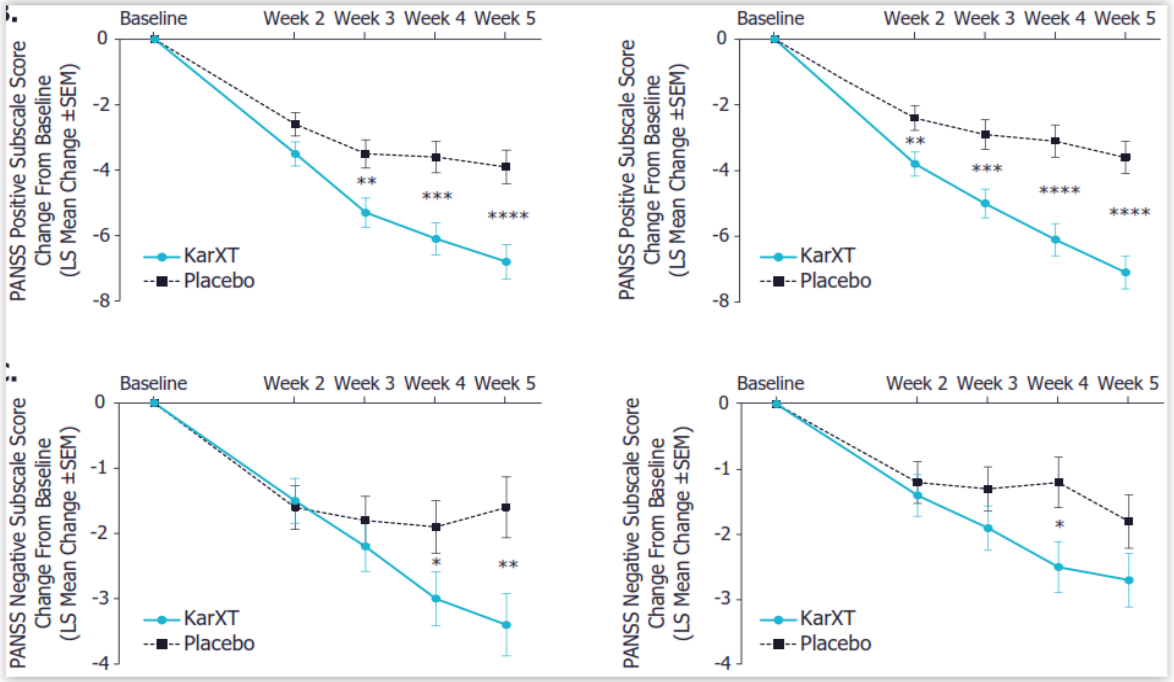
***P*<0.05; ****P*<0.01; *****P*<0.0001.

Efficacy analyses performed in modified intent-to-treat population.

LS = lease squares; PANSS = positive and negative syndrome scale; SEM = standard error of the mean

Brannan SK, et al. Poster presented at the 2023 American Society of Clinical Psychopharmacology (ASCP) Annual Meeting, May 30-June 2, 2023, Miami, Florida.

KarXT Phase EMERGENT-2 and EMERGENT-3: Change in PANSS Positive and PANSS Negative Scale Score From Baseline to Week 5



Brannan SK, et al. Poster presented at the 2023 American Society of Clinical Psychopharmacology (ASCP) Annual Meeting, May 30-June 2, 2023, Miami, Florida.

KarXT Phase EMERGENT-1, EMERGENT-2 and EMERGENT-3: Treatment Emergent Adverse Effects from Baseline to Week 5

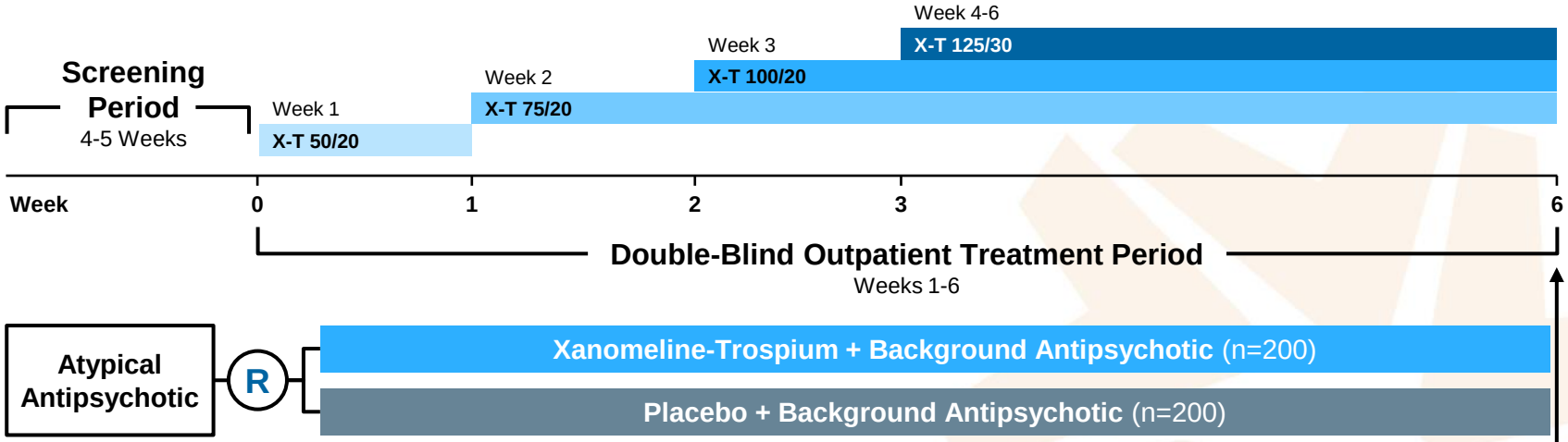
Table 2. Safety and Tolerability During the 5-Week Treatment Period (Safety Population): Pooled Results from EMERGENT-1. EMERGENT-2, and EMERGENT-3

Variable (%)	KarXT (n=340)	Placebo (n=343)
Any TEAE	67.9	51.3
Serious TEAE[a]	1.2	0.6
TEAE leading to discontinuation	5.6	4.7
TEAE occurring in ≥5% of people in the KarXT group		
Nausea	18.5	3.8
Constipation	17.1	6.1
Dyspepsia	15.3	4.7
Vomiting	13.5	1.7
Headache	10.9	10.2
Hypertension[b]	6.2	1.2
Dry mouth	5.0	1.5

a. In EMERGENT-1, 1 serious TEAE of increased psychosis occurred in the KarXT group. In EMERGENT-2, serious TEAEs were 2 cases of suicidal ideation in the KarXT group, 1 case of appendicitis in the placebo group, and 1 case of worsening of schizophrenia in the placebo group. In EMERGENT-3, 1 serious TEAE of gastro esophageal reflux disease occurred in the KarXT group.
b. Hypertension is the MedDRA preferred term and is not necessarily reflective of clinical hypertension.
MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
Brannan SK, et al. Poster presented at the 2023 American Society of Clinical Psychopharmacology (ASCP) Annual Meeting, May 30-June 2, 2023, Miami, Florida.

Potential for Xanomeline-Trospium as Adjunctive Treatment in Schizophrenia

Xanomeline-Trospium as Adjunct for Inadequately Controlled Schizophrenia (ARISE)



- Flexible dose of X-T; optional increase to 100/20 BID or 125/30 BID based on tolerability and clinical response
- Fixed dose of background antipsychotic (risperidone, paliperidone, aripiprazole, ziprasidone, or lurasidone)

Option to enroll in X-T 52-week open-label extension

Must have PANSS total score ≥70 to enter study

Primary endpoint: change from baseline to week 6 in PANSS total score

Estimated Completion October 2024

Clinicaltrials.gov. A Study to Assess Efficacy and Safety of Adjunctive KarXT in Subjects With Inadequately Controlled Symptoms of Schizophrenia (ARISE). Accessed August 22, 2023.https://clinicaltrials.gov/ct2/show/NCT05145413.

Other Muscarinic Agents in Development

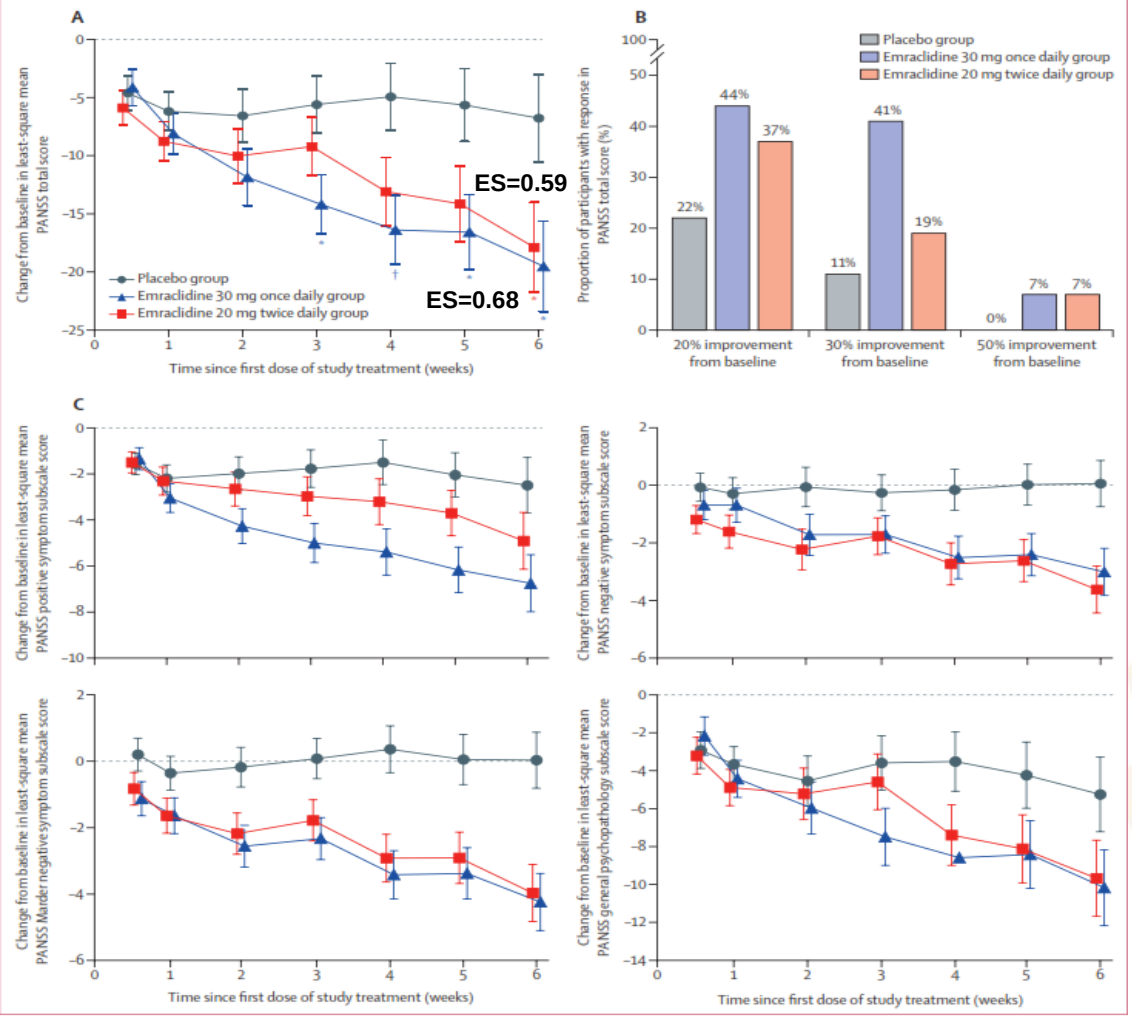


Figure 3: **PANSS scores in participants in part B**
(A) Change in mean PANSS total over time. (B) Proportion of participants with a response in PANSS score. (C) Change in PANSS subscale scores over time. Error bars show SE. PANSS=Positive and Negative Syndrome Scale. *Nominal p<0·05. †Nominal p<0·01.

Emraclidine (CVL-231) M4 Positive Allosteric Modulator: PANSS-Based Efficacy Results From a Phase 1B Study

Krystal JH, et al. *Lancet.* 2023 Dec 17;400(10369):2210-2220.

Emraclidine (CVL-231) M4 Positive Allosteric Modulator: Adverse Effect Results in Part B of a Phase 1B Study

n (%)	Placebo Group (n=27)	Emraclidine 30 mg Once Daily Group (n=27)	Emraclidine 20 mg Twice Daily Group (n=27)
Any adverse event	14 (52%)	14 (52%)	15 (56%)
Adverse events related to study drug	10 (37%)	7 (26%)	12 (44%)
Adverse events of special interest	3 (11%)	2 (7%)	4 (15%)
Serious adverse events	0	2 (7%)	1 (4%)
Adverse events leading to study discontinuation	0	2 (7%)	1 (4%)
Adverse events that occurred in at least 5% of participants receiving emraclidine where percent incidence was greater with emraclidine than with placebo			
Headache	7 (26%)	8 (30%)	7 (26%)
Nausea	1 (4%)	2 (7%)	2 (7%)
Back pain	1 (4%)	2 (7%)	1 (4%)
Blood creatinine phosphokinase increased	0	1 (4%)	2 (7%)
Dizziness	0	1 (4%)	2 (7%)
Dry mouth	0	3 (11%)	0
Somnolence	0	1 (4%)	2 (7%)

Krystal JH, et al. *Lancet*. 2023 Dec 17;400(10369):2210-2220.

NBI-1117568: Selective M_4 Agonist

Phase 1a study in 120 healthy volunteers completed in 2019

- No serious adverse events or typical muscarinic side effects reported
- Some cardiovascular effects observed
- Excluded CYP2D6 poor metabolizers and use of CYP2D6 inhibitors

Phase 2 study for treatment of adults with schizophrenia scheduled to start in late 2022

Sosei Heptares. Regains Worldwide Rights to Muscarinic Agonist Programs. Accessed 8/6/22. https://soseiheptares.com/uploads/financial_presentations/2021.01.05%20Muscarinic%20Regains_EN_FINAL.pdf. Neurocrine Biosciences. Accessed 8/6/22. https://neurocrine.gcs-web.com/news-releases/news-release-details/neurocrine-biosciences-reports-second-quarter-2022-financial. ClinicalTrials.gov. A Two-Part Study to Assess Safety, PK, PD, and Food Effect of Oral HTL0016878. Accessed 8/6/22. https://clinicaltrials.gov/ct2/show/NCT03244228.

Conclusions

1. M_4 (± M_1) agonists reduce psychosis without the risk of D_2-related movement disorders and metabolic adverse effects by decreasing presynaptic dopamine release
2. M_4 agonism reduces presynaptic dopamine via “bottom-up” regulation from the midbrain to the striatum. M_1 agonism contributes to antipsychotic effects in a “top down” fashion from the cortex to the striatum.
3. One M_4/M_1 agonist (in combination with a peripheral anticholinergic) has successfully completed three adequate and well-controlled studies
4. Two other medications acting on M_4 are advancing in clinical trials.

Key Learning Points

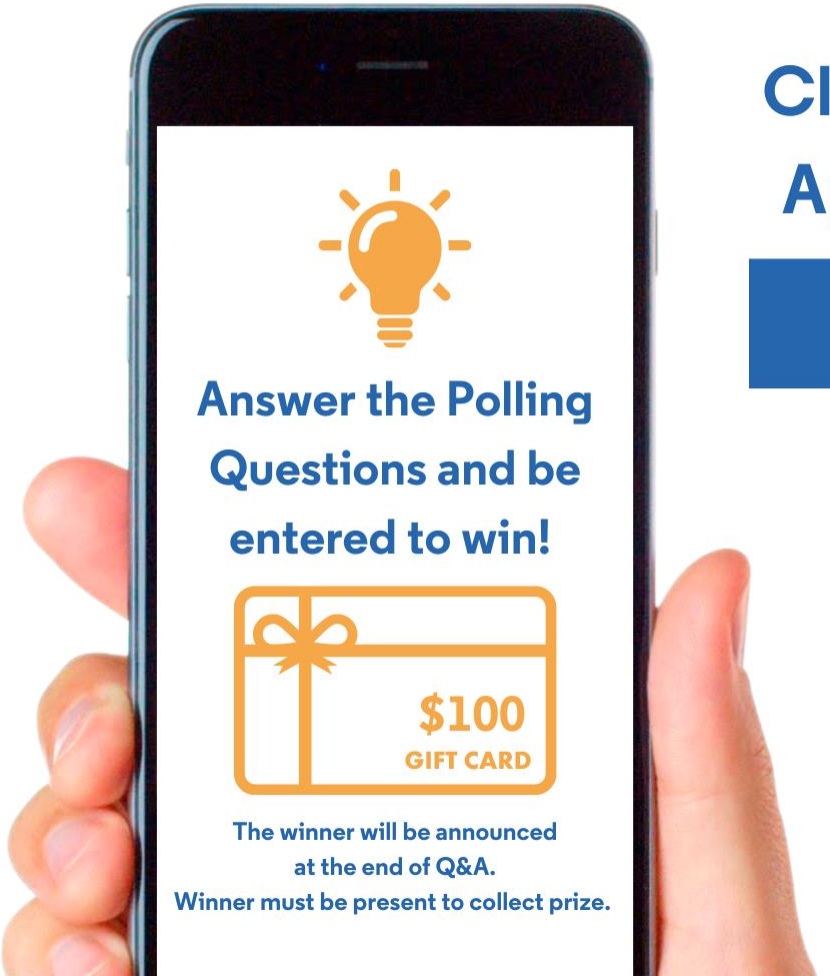
- The muscarinic cholinergic system modulates dopamine as well as other key neurotransmitter systems in the brain
- Peripherally, muscarinic receptors regulate respiration, pulse, blood pressure and gastrointestinal functioning
- **Xanomeline/trospium, a combination of an M1/M4 preferring muscarinic agonist** plus a peripherally restricted anticholinergic to buffer peripheral pro-cholinergic side effects has 3 positive placebo-controlled trials with effect sizes of 0.60, 0.61 and 0.75 at 5 weeks compared to placebo on total PANSS

Key Learning Points (continued)

- Adverse effects are pro- and anticholinergic in nature, mild to moderate in severity, emerge mostly in the first 3 weeks and are mostly transient, not leading to greater treatment discontinuation due to adverse effects than placebo
- Emraclidine, an M4 positive allosteric modulator, also has a positive phase 1 B study vs placebo
- In the EMERGENT clinical trials, xanomeline-tropsium was associated with improvements in **both positive and negative symptoms and overall illness severity**
- Muscarinic agonists may be the next generation of antipsychotic agents

Practical Take-Aways

- Several mechanisms whereby striatal dysfunction could contribute to the clinical manifestations of the schizophrenia.
- Schizophrenia is a heterogeneous disorder, and no single brain region or neurotransmitter is likely to be able to account for all symptoms in all patients.
- Therefore, it is an exciting to be part of an ever-changing journey to find the best treatment options for our patients



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DAVIDSON A

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